Vol. 14 NOVEMBER, 1937 No. 5

THE AMERICAN HEART JOURNAL

A JOURNAL FOR THE STUDY OF THE CIRCULATION

PUBLISHED MONTHLY
UNDER THE EDITORIAL DIRECTION OF
THE AMERICAN HEART ASSOCIATION

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523-25 PINE BLVD., ST. LOUIS, U. S. A.

CONTENTS ON INSIDE COVER

The American Heart Journal

CONTENTS FOR NOVEMBER, 1937

Original Communications

Department of Reviews and Abstracts

Vol. 14, No. 5, November, 1937. American Heart Journal is published monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, Canada, $8.50 a year; Foreign, $9.50. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879.

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Original Communications

ACUTE AND CHRONIC COMPRESSION OF THE HEART*

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PART I. COMPRESSION OF THE HEART

THE compressed heart produces a distinct clinical entity that deserves recognition. The correct concept of cardiac compression has been hidden by a confusing medical nomenclature. It has been hidden also by an incorrect physiological hypothesis. The treatment of the compressed heart is surgical, but correct diagnosis is a prerequisite to the operation.

The compressed heart is a small quiet organ. It cannot undergo dilatation. It cannot undergo hypertrophy. It is the exact opposite of the dilated hypertrophic heart. The anatomical agent producing the compression prohibits the heart from receiving its normal quota of blood for each systole. In as much as it receives a subnormal quota of blood, it actually pumps out a subnormal quota of blood, and the work load of the heart is reduced. The heart can do nothing about this reduction in work and it is forced to play a passive rôle in pumping what blood it receives. I believe that the heart can and actually does undergo atrophy of disuse in the compression diseases. It undergoes disuse atrophy much as any other muscle undergoes disuse atrophy when its work is reduced. After the compression agent has been removed by operation, the heart, like skeletal muscle, requires time to regain its normal strength. Indeed, in chronic cases the compression agent is sometimes removed completely with little improvement in the circulation noticeable after operation. The venous pressure may remain elevated and diuresis may not take place for days or weeks after operation. This delay in recovery I believe is due to the disuse atrophy suffered by the heart.

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Aided by a grant from the Josiah Macy, Jr. Foundation.

Presented at the meeting of the American Heart Association, Section for the Study of the Cardiac Diseases, at Atlantic City, June 8, 1937.

The compressed heart does not waste any of its energy as do many of the dilated, hypertrophic hearts. It functions efficiently although it is not allowed to function adequately. The cardiac valves in the compression diseases are normal. There are no murmurs. The only way in which the valves can become involved is for the insufficiency or stenosis to develop independently of the compression. The efficient, although inadequate, action of the heart is an important point in diagnosis. As the compression develops, the systolic-diastolic excursion of the heart is reduced. Sometimes no trace of pulsation can be seen over the precordium. This observation in itself is sometimes sufficient to enable one to make a differential diagnosis between compression and other forms of failure. It should save the surgeon the embarrassment of operating upon the dilated, hypertrophic, failing heart. Reduction in the amplitude of the heart beat can be seen by fluoroscopic examination. This examination is helpful not only in making the diagnosis of the condition but also in giving the surgeon important information concerning the operation. By it the surgeon sometimes can determine the nature of the compression agent, whether it is fluid, scar tissue, or tumor. He can also determine whether the operative approach should be to the right or to the left of the sternum. A record of the cardiac excursion can be made by the roentgen kymograph film. On the basis of the discussion so far it is clear that the compressed heart should be regarded as a small quiet organ. Cardiac compression has many other points of interest.

Let us now consider the flow of blood from the venae cavae into the heart. Let us consider the pressures exerted upon the venae cavae as they penetrate the pericardial cavity. These pressures under normal conditions are negative or less than the pressure of atmosphere. Now, if the pressure in the pericardial cavity is rapidly increased, as by the collection of blood, the venae cavae and the right auricle are immediately collapsed and the forward movement of blood is brought to a standstill. This condition exists until the pressure within the venous system builds itself up to a level high enough to break through the intrapericardial barrier. Blood then enters the heart. A delicate play of pressures exists between intrapericardial pressure and intravenous pressure. When the former increases, the latter must increase. Otherwise the patient dies. The pressure upon the intrapericardial structures can go up to certain definite levels. These levels are determined only by the heights to which the venous pressure can rise. The compression force upon the heart can never remain at a higher level than the pressure in the venae cavae. This statement can be considered as a physiological law. When the heart is acutely compressed, as occurs when a myocardial infarct or contusion ruptures, the venous pressure cannot rise above 15 or 20 cm. of water, and this is the fatal level in all cases of acute compression.

A pressure differential, so necessary to life, can be reestablished in two ways. One is to raise the venous pressure, the other is to reduce the compression. The venous pressure can be elevated to new high levels by the addition of fluid to the venous system. This point is of practical importance and may be applied in patients bleeding from the heart while preparation for operation is being made. In experiments in which a fatal compression level has been reached, the venous pressure can be promptly elevated to 25 or 30 cm. by the intravenous injection of fluid. In such experiments the arterial pulse returns and life can be prolonged.

The other signs and symptoms of acute cardiac compression are obvious. The veins are filled with blood. The venous pressure rises to 15 or 20 cm. The liver has not had time to enlarge. For the same reason ascites and subcutaneous edema are not present. The arterial circulation is weak and the arterial pressure falls. The mental anguish, excitement, or unconsciousness comes from cerebral anoxemia. The skin grows cool and moist.

Chronic compression of the heart produces a different picture. I produced chronic compression by the introduction of Dakin's solution into the pericardial cavity.[1, 2] This chemical irritant sometimes brought about a slowly forming accumulation of bloody fluid in the pericardial cavity without adhesions and produced the clinical picture of chronic compression. Sometimes the Dakin's solution brought about scar tissue formation on the epicardium and in the pericardium which in turn underwent contracture and compressed the heart. Experimentally it was found that the heart could tolerate a higher degree of compression if the compression developed slowly than if it developed acutely. In human patients the compression force may rise to remarkable levels.[3] In my series of patients the greatest compression force was from 40 to 45 cm. of water. It is interesting to speculate concerning the adaptation that makes such high compression forces possible. Why will a compression of 15 to 20 cm. kill when applied acutely, and why can 40 to 45 cm. be tolerated in the chronic conditions? The explanation lies in the venous pressure levels. There is not sufficient blood in the vascular system to elevate venous pressure above 15 to 20 cm. in response to acute compression. In the chronic condition we have some evidence to show than an increase in the circulating blood volume takes place.* Another possible cause in the elevation of venous pressure is brought about by the accumulation of fluid that slowly forms in the tissues and serous cavities. This fluid compresses the peripheral vascular tree to some extent and elevates the venous pressure.

*Some of these measurements were made on experimental animals, others on patients with compression. The data are not complete and are not to be considered as final because we have been having difficulty in obtaining satisfactory admixture of dye with the slowly moving blood. Also the presence of bile pigments in the blood in cases of chronic compression is a source of error in making colorimetric determinations.

The clinical manifestations of chronic compression of the heart are produced by venous stasis and a reduced arterial circulation. The veins are distended and sometimes elongated. They may stand out like goose quills. Cyanosis, ascites, enlargement of the liver and spleen, subcutaneous edema, varicose veins, hemorrhoids, hydrothorax, and pulmonary edema are all expressions of venous stasis. The liver becomes cirrhotic in response to long continued circulatory stasis. The liver and spleen may be coated with a fibrinous or fibrous exudate and the peritoneum may be thickened. These alterations in the abdomen are not infectious in origin nor are they tuberculous, as was formerly thought. They were present in our experiments and are due to venous stasis. Weakness, loss of subcutaneous fat, and retardation of growth are due to a reduction in arterial blood flow. Pulsus paradoxus is frequently present. The systolic pressure is usually 100 and the diastolic 80 mm. of mercury. The pulse pressure is about 20 mm. of mercury. Fixation of the heart to the sternum or to other structures has no diagnostic or therapeutic significance. Low voltage and slurring of the QRS complex are usually seen in the electrocardiogram. Fixation of electrical axis may or may not be present.

The diagnosis of cardiac compression should not be difficult. I have assembled two triads that should be helpful in the diagnosis of these conditions. The triad for acute compression of the heart (Fig. 1) is (1) a small quiet heart, (2) a rising venous pressure, and (3) a falling arterial pressure. The triad for chronic compression of the heart (Fig. 2) is (1) a small quiet heart, (2) a high venous pressure, and (3) ascites and enlargement of the liver. These triads cannot be wrong. Difficulties come in recognizing the small quiet heart. To some clinicians the small quiet heart is an unknown concept.

There are two reasons for this obscurity. One is the confusing medical nomenclature. Such terms as adhesive pericarditis, constrictive pericarditis, chronic obliterative pericarditis, concretio pericardii, symphysis cardiaca, pericarditic pseudocirrhosis of the liver, mediastino-pericarditis, Pick's disease, Concato's disease, and polyserositis are confusing. To quote from one of our text books: "This form of chronic peritonitis may be a part of a polyserositis (Concato's disease) and is especially often associated with chronic indurative mediastinopericarditis, of which Pick's pericardial pseudocirrhosis is a part. . . . The physical signs are those of ascites. . . The coincidence of the signs of ascites with chronic obliterative pericarditis or with arteriolar nephropathy help in making the diagnosis." Such medical verbiage is confusing and should be dropped from our present-day text books of medicine.

The other cause for confusion lies in the general acceptance of an incorrect physiological hypothesis, namely, the belief that adhesions to the heart play a rôle in producing failure, dilatation, and hypertrophy of the heart. I feel secure in stating that adhesions to the heart do

not produce dilatation, failure, or hypertrophy of the heart. Adhesions play no part in the production of the compression syndromes. When present, adhesions are silent and incidental findings and produce no circulatory trouble whatsoever unless the heart is acutely angulated or twisted. Our experimental and clinical evidence for these statements is conclusive and leaves no room for doubt.

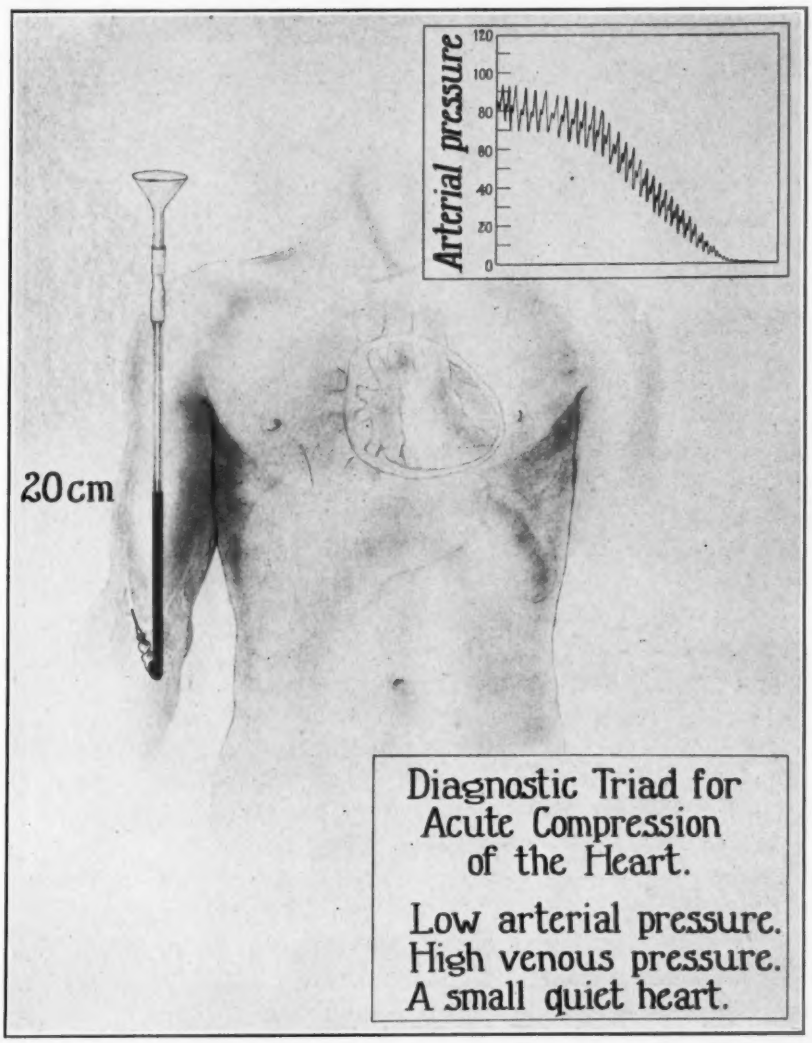

Fig. 1.—Acute compression of the heart. Note collapse of venae cavae and left auricle. The ventricles are smaller than normal because the heart contains a subnormal quantity of blood.

If our discussion is correct, this group of disorders no longer remains vague and intangible. The compressed heart becomes something definite both physiologically and clinically. It is just as definite as is a compressed brain. We are acquainted with the choked disc, headache, and

vomiting of a compressed brain. We should be equally well acquainted with the small, quiet, compressed heart. If our discussion on compression is acceptable, not only does the clinical picture become definite, but also the clinician is brought straightway to a consideration of the nature of the agent producing the compression, and, after the pathology of

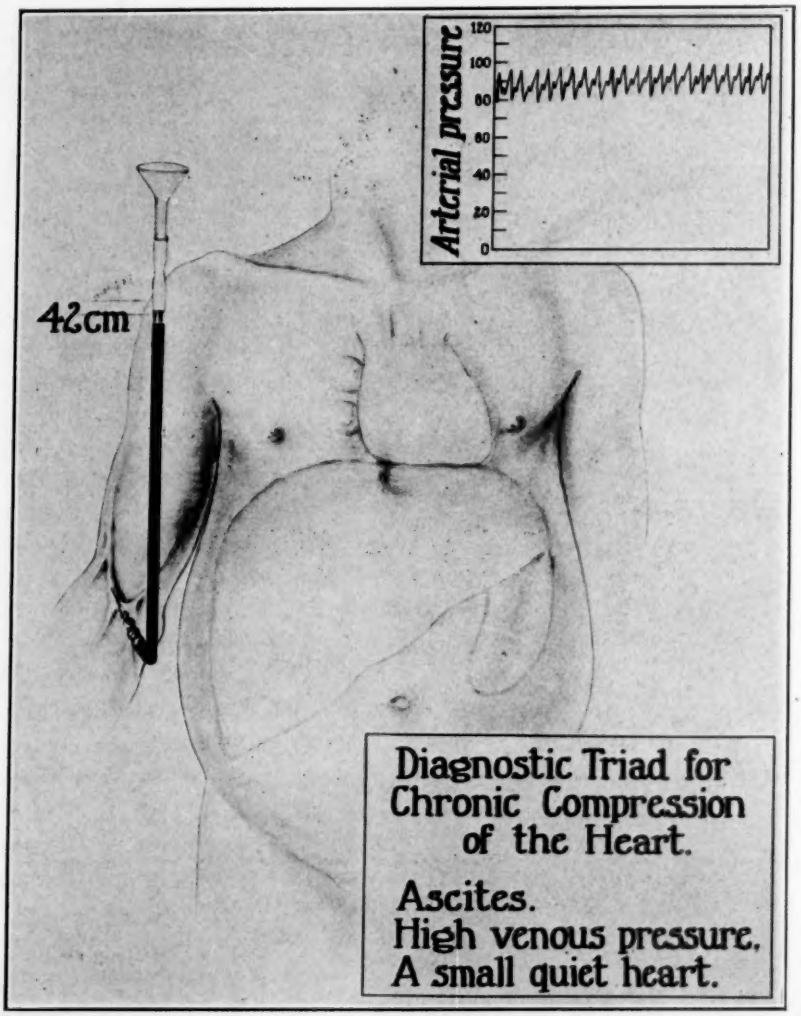

Fig. 2.—Chronic compression of the heart. The cardiopericardial silhouette must be differentiated from that of the heart alone. The heart is a small shrunken organ that undergoes disuse atrophy.

the lesion has been determined—and only after this has been determined—the proper treatment can be given.

Acute compression of the heart is always produced by a fluid. The fluid is usually blood but it can be a sterile exudate or pus. Only two types of acute cardiac compression have received surgical treatment.

The penetrating wound of the heart has been treated surgically, as has also the compression from pus in the pericardial cavity. So-called spontaneous rupture of auricles or ventricles has not been given the benefit of operation. Similarly acute compression produced by hemorrhage from a myocardial contusion or from a myocardial infarct has not been treated surgically. I can say with assurance that some of these are examples of neglect. Because some of these lesions have not been operated upon in the past is no adequate reason why they should not be operated upon in the future. The literature contains examples of slow hemorrhage, slow in terms of time required for getting ready to do the operation. The lesion responsible for the bleeding is not always extensive. Some of the lesions are amenable to suture or to reinforcement by a graft of pericardium. I feel confident that in the future a development will take place by which a larger proportion of these cases of acute compression will be treated by operation.

Chronic compression of the heart is produced by a variety of anatomical lesions. The compression agent may be fluid, scar tissue, neoplasm, or a combination of several of these lesions. The fluid may be sterile or infected. Hemorrhage from the heart may produce chronic compression, the bleeding being slow or intermittent. I had one patient with a sarcoma of the heart. The tumor bled intermittently and produced compression. Slow hemorrhage into the mediastinal cavity following the removal of a substernal goiter is known to have produced compression. Mediastinal effusions may produce compression. I have had a number of such effusions following operation on the heart. This complication is now cared for by establishing internal drainage into the pleural cavity at the time of operation. Some of the compressions are due to infections followed by the formation and contracture of scar tissue. The infection may be insidious and the development of the compression signs may be gradual and after they develop the patient may complain only of ascites and weakness. An extensive deposit of calcium may be laid down in the scar. In most of my cases of compression scars the nature of the organism could not be determined. Most of them, I believe, were pyogenic and only about 10 per cent were proved to be tuberculous. The chronic effusions may be tuberculous; from some of them no organisms can be recovered. One of my patients had mild compression signs from a non acid-fast tuberculous abscess lying over and compressing the venae cavae and right auricle. Two of my patients had compression from an invasion of parietal pericardium and mediastinum by sarcoma. In these patients the pericardium was thickened but not adherent to the heart. Another patient had a thickened parietal pericardium, bloody pericardial fluid, and an epicardial scar. In this case three factors were responsible in producing compression: the parietal pericardium was too thick to stretch; the fluid aided in the compression, and the epicardial scar had to be removed because it also

compressed the heart. The heart can be compressed or partially strangulated through a traumatic rupture of the parietal pericardium. The compression scars may be localized or generalized over the entire heart. The venae cavae and right auricle were compressed in some of our experiments. I have seen one specimen in which a band of calcified scar surrounded the two ventricles, there being no other involvement. In another patient a calcified ring of tissue surrounded the pulmonary artery.

The experiences obtained in the treatment of these conditions cannot be presented in this paper. It is needless for me to say that many of these patients with chronic cardiac compression can be cured by operation and the cures are permanent. The question has been raised as to whether adhesions form again after resection of a scar from the heart. Adhesions do form, but again may I add that adhesions play no part in the production of compression. If the infection has become quiescent before operation, if it has burned itself out so to speak, a thick scar which later undergoes contracture will not form again and the cure is permanent.

PART II. ADHESIONS TO THE HEART

Since the time of Auenbrugger, Corvisart, and Laënnec, we have been laboring in the dark concerning the subject of adhesions to the heart. It is generally believed that adhesions disturb the heart action and that they can produce dilatation, hypertrophy, and failure. The relationship between adhesions, on the one hand, and dilatation, hypertrophy, and failure of the heart, on the other hand, has been generally considered as one of cause and effect. Because of a belief in this causal relationship, medical men have been chagrined when they have not recognized adhesions in cases of failure. These diagnostic mistakes or omissions in cases of adhesions are not infrequent. As an aid in diagnosis Norris and Landis wrote as follows: "Whether cardiac murmurs are present or not, adhesive pericarditis is to be thought of in a young adult if there is a history of acute rheumatic fever followed by endocarditis, and, especially so if the cardiac failure is more marked or the cardiac enlargement more extensive than the endocardial damage seems to warrant. An additional point of some importance is the fact that in young individuals apparently suffering from endocarditis, an adherent pericardium is to be suspected when the heart does not respond to digitalis." Much has been written on the diagnosis of adhesive pericarditis. Retraction of the chest wall, Broadbent's sign, friction rubs, and fixation of the electrical axis are all supposed to mean something in the way of diagnosis. There are many signs described for the diagnosis of pericardial diseases. The clinician has even listened for and heard the "pericardial knock." In

spite of all these diagnostic endeavors, why is it that the diagnosis of adhesive pericarditis is little more accurate than a guess? The answer, although fundamental, is simple.

From 1923 to the present time I have continuously had in progress some type of recovery experiment on the heart and pericardium. Regardless of the purpose of these experimental studies, adhesions to one or more of the structures adjacent to the heart were encountered in practically every experiment. In 1931 I reported the results of a special study of intrapericardial and extrapericardial adhesions produced experimentally.[4] The conclusions arrived at were that such adhesions did not produce circulatory embarrassment, that they did not produce hypertrophy, dilatation, or failure of the heart. During the past six years we have been deliberately grafting tissues upon the heart for the purpose of producing a new blood supply to the myocardium.[5] The tissues grafted upon the heart were parietal pericardium, mediastinal fat, pedicle grafts of muscle from the chest wall, and omentum. In all I would estimate that well over a thousand experiments on the heart have been carried out. Again on the basis of this experience it was my impression that adhesions produced little or no disturbance to the heart. Acute angulation or torsion of the heart on its long axis did disturb the heart and produced changes in arterial and venous pressures, but the ordinary pull upon chest wall or diaphragm was well tolerated. In 1933 Hosler and Williams[6] began a series of carefully controlled experiments for the purpose of making more accurate measurements on this subject. They divided their experiments into three groups: (1) extrapericardial, i.e., adhesions between parietal pericardium and diaphragm; (2) intrapericardial, or adhesions between parietal pericardium and heart; and (3) combined, in which heart, pericardium and diaphragm were united. In one of these experiments the pull was so great as to produce a sacculation or diverticulum of the right ventricular cavity. The animals were exercised upon a tread mill and were observed over a period of two years. Cardiac hypertrophy was not found in any of these experiments either grossly or microscopically. Likewise failure and dilatation were not found. Hosler analyzed the autopsy material at the University Hospitals and found 75 instances of extensive pericardial adhesions in 4,400 autopsies. This group of 75 was divided into 54 in which hypertrophy was present and 21 in which hypertrophy was absent. In each of the 54 cases there was concomitant heart disease or vascular disease which in itself could account for the hypertrophy. Almost without exception the largest hearts were the seat of rheumatic pancarditis. An analysis of the 21 hearts with extensive adhesions but without hypertrophy showed that these hearts were free from valvular, myocardial, or vascular disease in all except one case and this showed mild rheumatic heart disease. I believe that we can be positive in

asserting that adhesions to the heart do not produce dilatation of the heart, failure of the heart, or hypertrophy of the heart. The only way in which adhesions can impair the circulation is by producing acute angulation of the heart from its normal axis or by producing torsion of the heart either clockwise or counterclockwise in the long axis of the heart. Such acute dislocations of the heart are readily produced when the heart is exposed at operation. They are rarely encountered in patients.

The exact mechanism by which angulation and torsion of the heart disturb the circulation needs further study. It is our opinion that the great vessels at the base of the heart are primarily involved. However, neurogenic disturbances resulting in changes in heart rate seem to be possible as demonstrated by a patient whom we now have under observation. It should be pointed out that angulation and torsion of the heart interfere with the circulation in a manner entirely different from energy-loss by pulling upon chest wall or diaphragm.

On the assumption that the heart wastes energy in pulling upon chest wall through adhesions, attempts have been made to correct this condition by operation. Let us assume that the heart has become adherent to parietal pericardium and that the pericardium has become adherent to the chest wall.* As the heart beats, the chest wall is pulled upon and this movement appears to be a waste of energy. When the heart begins to increase in size as it frequently does in those conditions in which adhesions appear (rheumatic heart disease) the waste of energy is considered as a cause of the hypertrophy and enlargement. On this assumption the next step is towards correction. Two possibilities exist. One is to sever the central end of the adhesion, i.e., the heart end. The other is to relax the particular part of the chest wall that is pulled upon by removing the ribs from this particular area. The first alternative has never been utilized, but in 1902 the second idea was applied and the Brauer[8] operation came into being. This operation has been reported in over a hundred cases and is incorrectly called a "cardiolysis."

What results have been obtained by this operation?[9] In analyzing the results I am reminded of a patient whom I saw about five years ago. He had panrheumatic heart disease with adhesions. He was critically ill with ascites, hydrothorax, cyanosis, etc., and any type of operation was out of the question. He was sent home to die. Today this patient is remarkably well and all signs of failure have disappeared. He leads an active life. If the operation had been done and if he had survived it, it would be considered that an excellent result had been obtained from

*Broadbent[7] noticed that even if the heart were not directly adherent to the chest wall a pull upon the chest wall, nevertheless, could be effected by pulling upon the diaphragm.

the Brauer operation. The results of the operation in general cannot be analyzed with any degree of accuracy. There is no similar control group for comparison. If I might express an opinion, I would say that the extra bed rest and attention afforded these patients before and after operation did them more good than the operation itself. Even this statement implies that the operation did some good and of this I am skeptical.

In conclusion, I believe that adhesions to the heart are silent and incidental, that there may be no reason for their recognition clinically, and that there is no reason to operate for their correction.

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THE USE OF MERCUPURIN IN THE TREATMENT OF CONGESTIVE HEART FAILURE AND IN THE MOBILIZATION OF EXCESS BODY FLUID*

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WE ARE so frequently confronted with manifestations of congestive heart failure that methods of combating them are a matter of great concern. That the methods are *at times* and indeed *finally* unsuccessful is ample evidence that we have not yet found the infallible diuretic. It is important therefore for us to test rigidly and impartially any new diuretic drug that gives promise of being beneficial.

In heart failure of the congestive type, and in certain other unrelated conditions in which there is accumulation of excess fluid in the body, such as cirrhosis of the liver exhibiting ascites, reduction in the amount of excess fluid is commonly followed by relief of symptoms. This beneficial effect is often attained by the administration of drugs possessing diuretic action. Since the introduction of salyrgan by Bernheim in 1924,[1] this organic mercurial diuretic has been widely used in the treatment of heart failure of the congestive type and cirrhosis of the liver exhibiting ascites; it is now recognized to be a potent drug of low toxicity.

In an attempt to make an even more potent and less toxic diuretic than salyrgan, von Issekutz and von Végh[2] in 1928 described a new organic mercurial diuretic which they called novurit. Novurit differed from salyrgan in two respects: first, the mercury containing radical was a different organic substance; and second, it contained theophyllin, which was said to be chemically bound to the mercurial compound. Von Issekutz and von Végh claimed that the diuretic effect of novurit in rabbits was considerably greater than that of salyrgan and also that it was only one-half as toxic in rats. Since the introduction of novurit it has been shown by Herrmann, Schwab, Stone, and Marr,[3] that the combination of theophyllin and a mercurial diuretic exerts a diuretic action greater than that of either of the drugs when given alone. Furthermore, DeGraff and Batterman[4] have observed that the presence of theophyllin at the site of injection of mercurial diuretics tends to prevent the local toxic effects of the mercurial drug on the tissues. In the light of these observations a drug containing theophyllin in chemical combination with a mercurial compound might possess certain advantages not inherent in or possessed by salyrgan.

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Novurit is said to contain mercury 0.0393 gm. per cubic centimeter, an amount approximately identical with that in salyrgan. In addition, it contains 5 per cent of theophyllin, 3.5 per cent of which is said to be chemically bound to the organic mercury compound. During the past two or three years novurit has been sold in the United States under the proprietary name "mercupurin."* Novurit and mercupurin are names for the same substance.

Clinical experience with mercupurin has been recorded within the past seven years by Hahn,[5] Popper,[6, 7] Saxl,[8] Spengler,[9] Engel and Epstein,[10] and Pratsicas,[11] abroad, and within the past two years by Crawford and McDaniel,[12] Fulton and Bryan,[13] Steuer and Wolpaw,[14] and DeGraff, Nadler, and Batterman[15] in the United States. The number of patients to whom these investigators gave mercupurin varied from three to sixty. Most of the patients were suffering from heart failure of the congestive type, a few from cirrhosis of the liver exhibiting ascites. None of these investigators gave more than a few injections to each patient. Toxic effects were not observed. Certain observers[8, 9, 10, 13, 14] were of the opinion that it was as satisfactory as salyrgan, while others[5, 6, 7, 11, 12, 15] found it more effective. In addition to the papers already quoted, there are many in the Slavic languages which were not available to us.

The effects of the administration of mercupurin to patients on the medical pavilions of the New York Hospital have been observed for one year. No effort was made to study the mechanism of action of mercupurin nor to compare directly the effect of mercupurin and that of salyrgan. The results of these observations under conditions similar to those in which the drug is commonly used form the subject of this report.

METHODS OF OBSERVATION

All patients were at rest in bed. With a few exceptions a diet containing two grams of salt was given. The intake of fluid was restricted to 1,200 c.c. a day in most instances. Occasionally a larger amount was given, usually because fever was present. Many of the patients suffering from heart failure of the congestive type received maintenance doses of digitalis daily and many of them were given theocalcin, theobromine sodiosalicylate, or aminophylline as well. The data forming the basis for this report comprise only those observations in which the diuretic effect of mercupurin could be isolated from the effects of other drugs if they were being given. Most patients received ammonium chloride, 3.0 gm. daily, at the same time. Patients were weighed daily before breakfast unless they were so ill that it appeared advisable to weigh them at intervals of several days instead. The intake of fluid and

*We have used in our studies mercupurin prepared by Campbell Products Inc., New York City.

output of urine were measured in twenty-four-hour periods. Since the apparent diuretic effect was the same whether the volume of urine or the loss of weight was selected as the criterion, the former, namely the volume of urine, was used as the measure of diuresis.

With the exception of one patient, Mrs. M. L., Case No. 4, who received the drug intramuscularly, it was given intravenously without dilution. It was given in the morning in order that the volume of urine excreted on the day of injection might represent the largest part of the diuretic effect. In most instances a trial dose of 1.0 c.c. was given, and followed after an interval of twenty-four hours by the usual therapeutic amount, 2.0 c.c. This amount was repeated at three-day intervals as long as there was indication for its use. The interval became longer as the accumulations of fluid decreased. The use of the drug was continued until improvement reached a satisfactory stage or until it failed to induce diuresis. In certain cases it was given at irregular intervals as it appeared to be indicated.

OBSERVATIONS

Four hundred thirty-eight injections were given to 66 patients presenting clinical evidence of accumulation of fluid in the tissues. Fifty-two of these exhibited heart failure of the congestive type. In them the etiology of the heart disease was rheumatic fever in 19 (Cases No. 1 to 16 inclusive, 59, 60, 61), arteriosclerosis in 13 (Cases No. 17 to 25 inclusive, 62-65), hypertension in 10 (Cases No. 26 to 35 inclusive), syphilis in 2 (Cases No. 36 and 37), pericardial disease in 6 (of these, 5 [Cases No. 38, 40-43] suffered from chronic constrictive pericarditis and 1 [Case No. 39] from recurrent pericardial effusion), and pulmonary fibrosis* in 2 (Cases No. 44 and 45). Nine patients (Cases No. 46 to 53 inclusive and 66) suffered from cirrhosis of the liver exhibiting ascites. Of the five patients remaining, 2 (Cases No. 54 and 55) exhibited the nephrotic stage of chronic glomerular nephritis, 1 (Case No. 56) hydrothorax and ascites of unknown etiology, another (Case No. 57) ascites as a consequence of tuberculosis of the peritoneum; and finally 1 (Case No. 58) exhibited hydrothorax and ascites secondary to carcinomatosis of the pleura and peritoneum respectively.

Patients received from 1 to 45 injections: forty-one received from 1 to 5 injections; twelve, from 6 to 10; seven, from 11 to 15; and three, from 16 to 20. Mrs. C. K., Case No. 46, received 29 injections in six months. Another patient, Mrs. A. R., Case No. 38, received 36 injections in twelve months, while another, Miss E. C., Case No. 39, received 45 injections in thirteen months. These two, as well as four others, were given mercupurin in the out-patient department after discharge from

*Pulmonary fibrosis was considered to be the etiological factor in those cases in which there was observed pulmonary emphysema, enlargement of the right ventricle, cyanosis out of proportion to the other evidences of heart failure, and lack of evidence of any one of the other more usual etiological factors.

the hospital. Evaluation of the effect of injections given in the outpatient department was made from a consideration of the occurrence of systemic toxic effects, of undesirable reactions at the site of injection, of the apparent effectiveness of the drug in preventing the reaccumulation of fluid, of a statement of the patient as to the diuretic effect, and finally in certain instances, of measurement by the patient of the volume of urine. The results of the injections given to patients in the outpatient department are not, however, included in the quantitative data recorded in Figs. 1 and 2, which form the basis for our analysis of the effectiveness of this drug.

Only 286 of the 438 injections appear to represent the diuretic effect of mercupurin uninfluenced by factors which might have altered the result obtained from the drug. That is to say, the results from 152 injections were discarded either because of incomplete data, or because the simultaneous administration of another drug did not permit us to

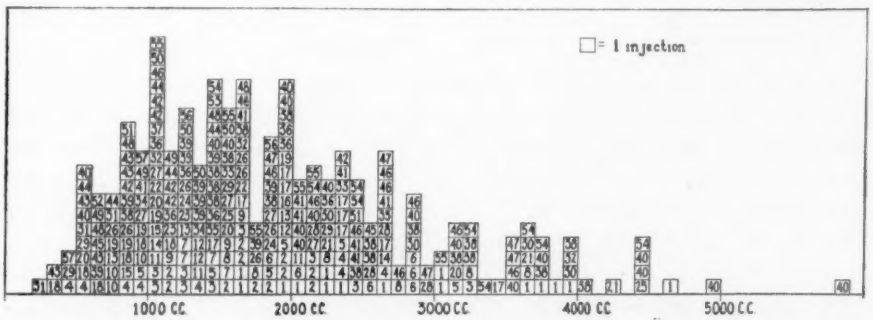

Fig. 1.—This figure represents a frequency distribution of the daily amounts of urine from 200 c.c. to 6,000 c.c. in 100 c.c. increments resulting from 286 injections of mercupurin in 57 patients. Each square represents 1 unit, that is to say, 1 injection. The numbers in the squares identify the patients. In patients numbers 1 to 16 inclusive and 59, 60, 61, the etiological diagnosis was rheumatic fever; in numbers 17 to 25 inclusive and 62-65, arteriosclerosis; in numbers 26 to 35 inclusive, hypertension; in numbers 36 and 37, syphilis; in numbers 38 to 43 inclusive, pericardial disease; in numbers 44 and 45, pulmonary fibrosis; in numbers 46 to 53 inclusive and 66, cirrhosis of the liver exhibiting ascites; in numbers 54 and 55, the nephrotic stage of chronic glomerular nephritis; in number 56, hydrothorax and ascites of unknown etiology; in number 57, ascites as a consequence of tuberculosis of the peritoneum; and in number 58, hydrothorax and ascites secondary to carcinomatosis of the pleura and peritoneum respectively.

make an estimate of the effect of mercupurin. The 286 injections which satisfy our criteria were given to 57 patients.

DISCUSSION OF RESULTS

Statistical analysis of the data relating to the 286 injections which satisfy our criteria yields more information about the results to be expected from giving mercupurin than can be obtained by the study of individual cases. For this analysis data have been arranged in the form of two frequency curves (Figs. 1 and 2). The general trends of diuretic effect appear from examination of each chart as a whole and the analysis of each as a frequency curve. From these curves also may

be observed the variation in effect in individual cases, as well as the influence of etiology on the diuretic effect.

For instance, it appears that the diuretic effect in the greatest number of the injections lies in the zone representing a diuresis of between 1,000 and 2,000 c.c. in twenty-four hours (Fig. 1). The output of urine on the day of injection, however, varied between extremes of 200 and 300 c.c. and 5,800 and 5,900 c.c. The following facts stand out: on one occasion only was a diuresis greater than 5,000 c.c. obtained; 8 injections given to 6 patients resulted in a diuresis of between 4,000 and 5,000 c.c., while 33 injections given to 15 patients yielded an output of urine of between 3,000 and 4,000 c.c., and 69 injections given to 28 patients gave a diuresis of between 2,000 and 3,000 c.c. A volume of urine less than 1,000 c.c. occurred with relative infrequency.

Analysis was made from another point of view: it appears that the most frequent effect of the drug was to increase the volume of urine on the day of injection from two to five times over that on the preceding day (Fig. 2); the extremes show at one end that the output of urine on the day of injection was occasionally less than the amount on the preceding day, and at the other end that it was 19 times that amount. It was uncommon for the urinary output to increase 10 times or more. Increases of from 5 to 10 times were observed in relatively few instances. Only 24 of 286 injections failed to produce any increase in the urinary output. From the distribution of numerals referring to patients in Figs. 1 and 2, it is apparent that in certain patients an injection might at one time produce marked diuresis and at another time be less effective. For example, Case No. 38 gave a number of responses of between 1,000 and 2,000 c.c., and also a number which lay between 3,000 and 4,000 c.c. In certain instances the variation in response appeared to be related to the amount of excess fluid present; in others it was not possible to attribute the difference in effect to this cause and we were unable to account for it. In other patients small diuretic responses were usually obtained, as for example Case No. 18, whose response was usually less than 1,000 c.c. In other patients, still, consistently good effects were obtained; for example, in Case No. 40 the diuresis was usually in excess of 3,000 c.c.

These data have been analyzed also with respect to the bearing of etiology on the effectiveness of this diuretic drug (Figs. 1 and 2). Five cases of chronic constrictive pericarditis (Cases No. 38, 40-43) as an etiological group, showed the best diuretic effect. There did not appear to be any significant difference in effect between cases of heart failure of the congestive type whether it was of rheumatic, of arteriosclerotic, or of hypertensive etiology. Nine cases of cirrhosis of the liver exhibiting ascites, as a group, showed smaller effects than any of the other etiological groups in which the number of cases was comparable; nevertheless, excellent diuresis was occasionally obtained in this group. For

example, Mrs. C. K., Case No. 46 (Fig. 7) usually responded to an injection by a urinary output of over 2,500 c.c. so that the drug was quite effective in preventing the recurrence of ascites. With respect to

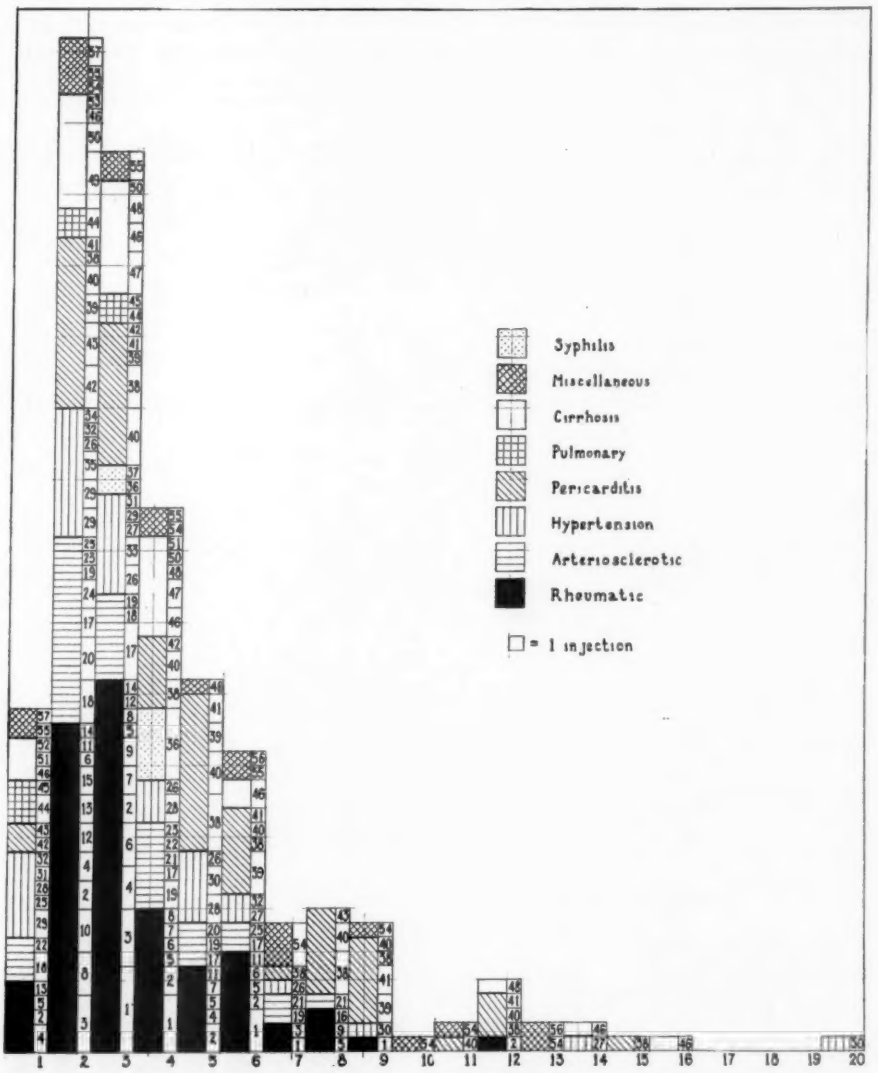

Fig. 2.—This figure represents a frequency distribution of the quantitative diuretic effect of mercupurin, calculated on the ratio of the urine output on the day of the injection to the day before injection. In it are recorded 286 injections given to 57 patients. The unit is one injection. The numbers, which are the same as in Fig. 1, are used to identify the patients. In the column parallel to the units in each quantitative rubric are placed symbols indicating the etiological diagnosis. In each column the same sequence of etiological classification is maintained.

the other etiological groups, namely syphilitic heart disease, pulmonary heart disease, and the miscellaneous group of 6 cases, the number of patients was too small to permit a general statement.

The diuretic effect of mercupurin is recorded in data secured from 5 patients illustrating as many etiological groups (Figs. 3 to 7).

In the case of Mr. J. H., Case No. 1, a white male, forty-eight years of age, the diagnoses* were: (a) rheumatic fever; (b) cardiac enlargement, mitral stenosis and insufficiency; (c) auricular fibrillation, and heart failure of the congestive type. He had suffered from dyspnea and ankle edema for twelve years before admission. He exhibited the following signs of heart failure: many moist râles at the bases of both lungs posteriorly, marked swelling of the liver, a small amount of fluid in the peritoneal cavity, and massive pitting edema of the lower legs and thighs. It was found that rest in bed and the administration of digitalis had little diuretic effect. Because auricular fibrillation was present, the use of digitalis was, however,

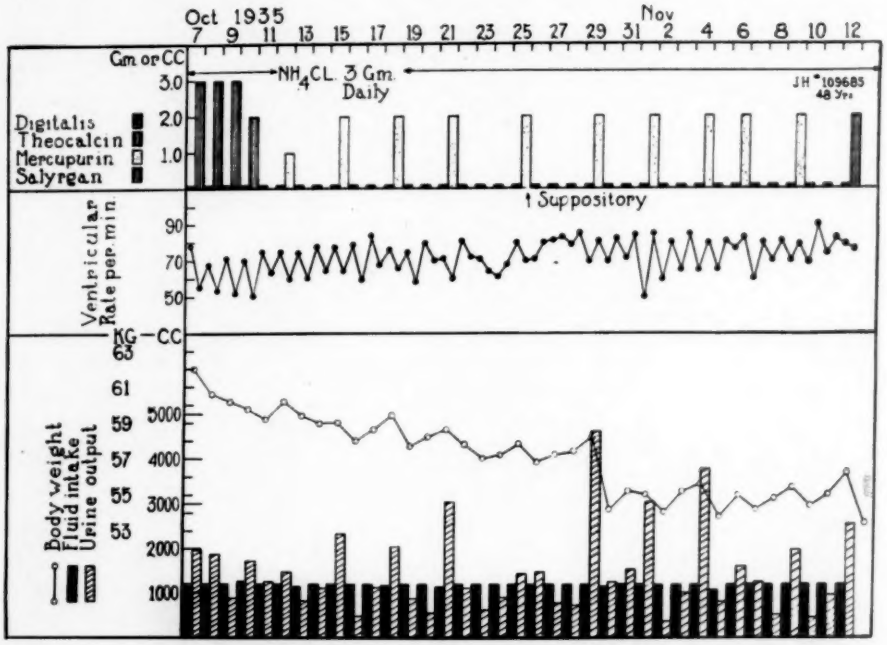

Fig. 3.—In this figure is represented the diuretic effect of mercupurin in the case of J. H., Case No. 1, suffering from rheumatic heart disease.

continued. On giving mercupurin, excellent diuresis, attaining 4,600 c.c. a day, was obtained (Fig. 3), associated with loss in body weight and the regression of the physical signs of heart failure.

Mr. W. W., Case No. 21, a white male, sixty-eight years of age, suffered from arteriosclerotic heart disease. The diagnoses were: (a) arteriosclerosis; (b) enlargement of the heart; (c) auricular fibrillation, and heart failure of the congestive type. He had experienced dyspnea, edema of the ankles, and precordial pain both on exertion and at rest for one and one-half years, and orthopnea and cough for two months. The following signs of congestive heart failure were observed: many moist râles at both lungs bases, a small amount of fluid in both pleural cavities, moderate swelling of the liver, and marked pitting edema of the lower legs, thighs, and sacral region. On the exhibition of rest in bed, digitalis, and theobromine sodiosalicylate

*The cardiac diagnoses in this paper conform to the nomenclature for cardiac diagnosis recommended by the American Heart Association, AM. HEART J., 2: 202, 1926-27.

no demonstrable change in the physical signs occurred. Injections of mercupurin were then given and induced a tremendous increase in the output of urine, which was as great as 4,200 c.c. a day (Fig. 4), accompanied by rapid decrease in the accumulation of fluid.

In the case of Mrs. C. C., Case No. 30, a white female, forty-three years of age, the diagnoses were as follows: (a) hypertension; (b) enlargement of the heart; (c) normal sinus rhythm, and heart failure of the congestive type. Hypertension was known to have been present for at least nine years, dyspnea, orthopnea, and ankle edema had been observed for three years, and during this period digitalis had been taken regularly. The signs of heart failure were as follows: many moist

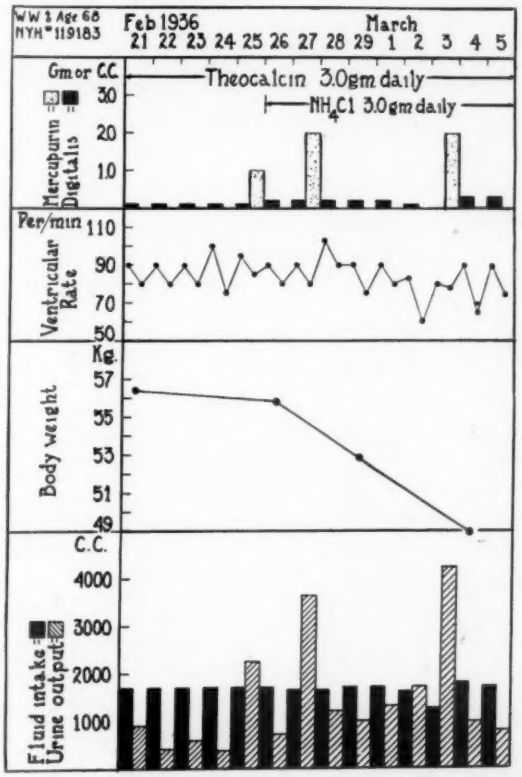

Fig. 4.—In this figure is represented the diuretic effect of mercupurin in W. W., Case No. 21, suffering from arteriosclerotic heart disease.

râles at the bases of both lungs, marked enlargement of the liver, and massive pitting edema of the lower legs, thighs, and sacral region. The administration of digitalis was continued. Because the output of urine remained low mercupurin was given also. It induced diuresis amounting to as much as 3,700 c.c. a day, and as a consequence the peripheral edema disappeared and the other signs of heart failure decreased; a satisfactory loss of weight was observed (Fig. 5).

The case of Mrs. P. A., Case No. 40, a white female, forty-four years of age, illustrates the effect of this drug in a patient suffering from chronic constrictive pericarditis of unknown etiology. Auricular fibrillation was present. She complained of swelling of the ankles for five months and swelling of the abdomen for two months before admission to the hospital. Fluid in both pleural cavities, moist râles

over the upper part of both lungs, marked enlargement of the liver, a large amount of ascites, and massive edema of both lower legs and thighs were the signs of heart failure. The exhibition of rest in bed, of restriction of fluid and salt, and of digitalis as well as theocalcin not only failed to reduce the accumulations of fluid

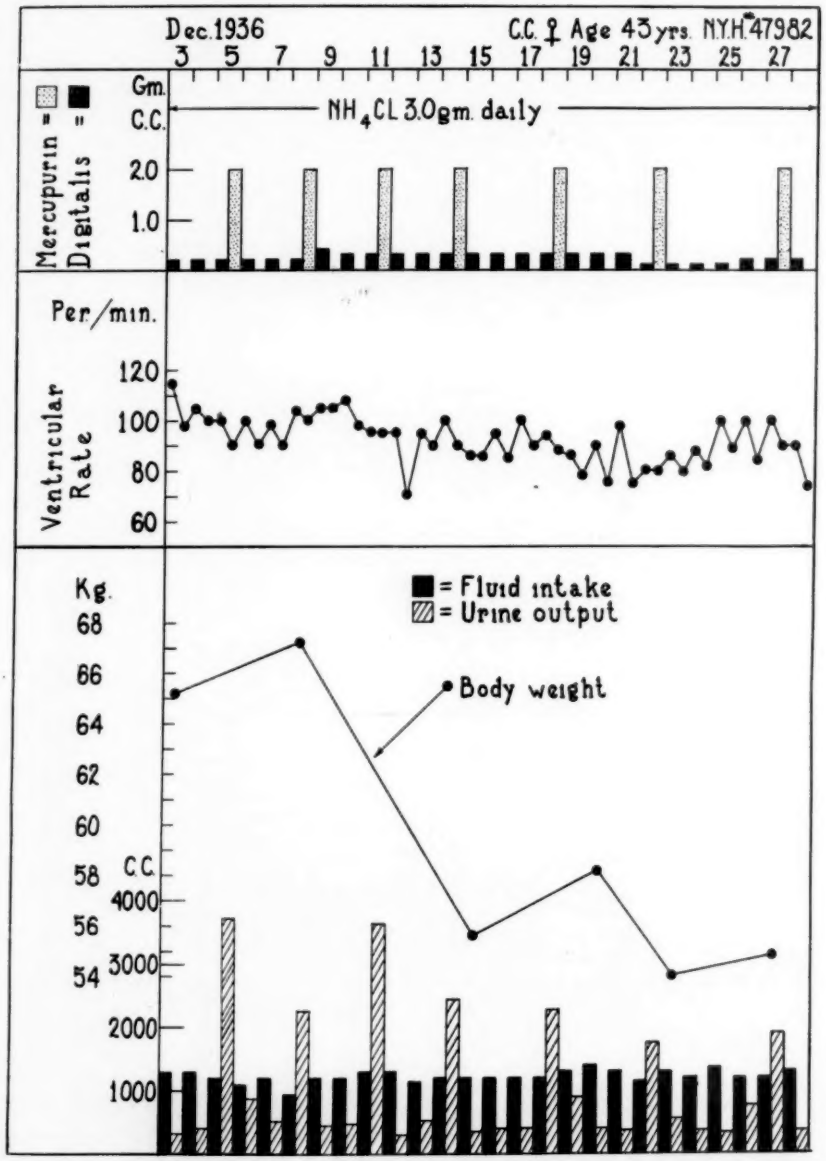

Fig. 5.—In this figure is shown the diuretic effect of mercupurin in C. C., Case No. 30, who suffered from hypertensive heart disease.

but were also ineffective in preventing further storage of it. When mercupurin was given at intervals of two or three days, excellent diuresis was obtained, the urinary output increasing to as much as 5,800 c.c. a day, the patient lost weight rapidly, and decrease in the clinical signs of heart failure was observed. The patient ap-

peared to gain weight in the intervals between the injections, so that it appeared that mercupurin alone was responsible for the failure of fluid to reaccumulate and weight to increase (Fig. 6).

The use of this drug in alcoholic cirrhosis of the liver when ascites is present is illustrated in the case of Mrs. C. K., Case No. 46, a white female, forty-four years of age (Fig. 7). On two previous admissions to the hospital the administration of salyrgan had proved ineffective in preventing the recurrence of ascites. When the patient came under our observation during her third admission she had been in the

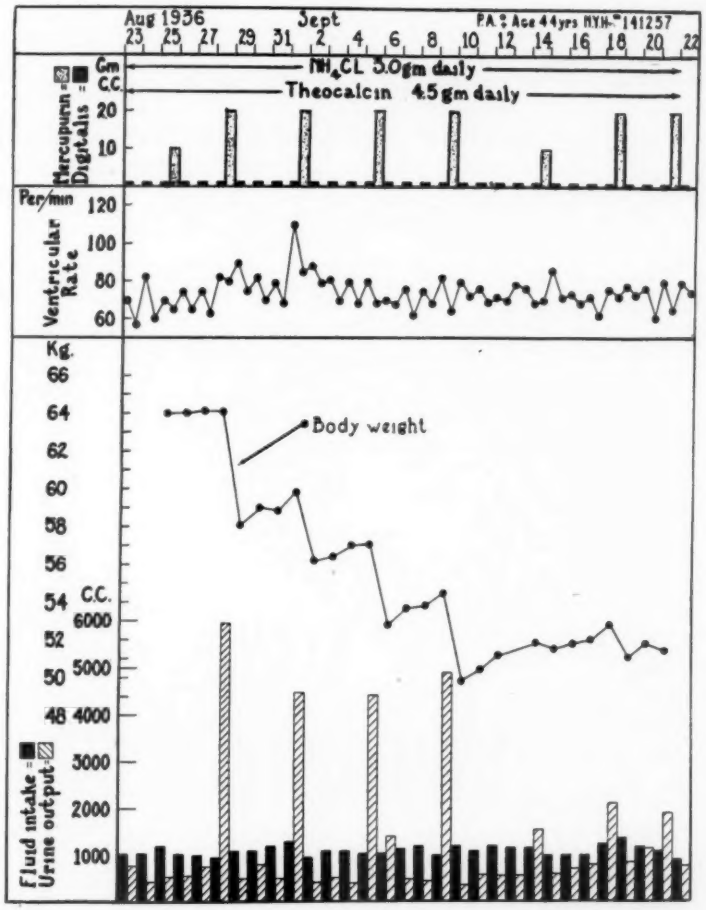

Fig. 6.—In this figure is represented the diuretic effect of mercupurin in the case of P. A., Case No. 40, suffering from chronic constrictive pericarditis. Ammonium chloride and theocalcin were given daily. Diuresis occurs on the days mercupurin was given.

hospital for twenty-one weeks. During this period it had been necessary to perform abdominal paracenteses at approximately ten-day intervals, and no decrease had been noted in the rapidity with which fluid recurred. A series of injections of mercupurin was then instituted and was found effective in preventing increase in the amount of ascites; the body weight remained relatively constant (Fig. 7). Mercupurin was then injected at weekly intervals for six months, both in the hospital and in the out-patient department. During this six months' period only four abdominal

paracenteses were required. The occasion for these arose in consequence of attempts to discontinue the use of mercupurin.

Certain observations are not brought out in the data presented in Figs. 1 and 2. For instance, 54 injections of mercupurin given to 31 patients gave diuresis which was definitely prolonged into the day following its administration. Its effect had disappeared on all occasions, however, by the end of forty-eight hours.

It was observed in general that the smallest diuretic effects occurred for the most part in patients in whom examination revealed little evi-

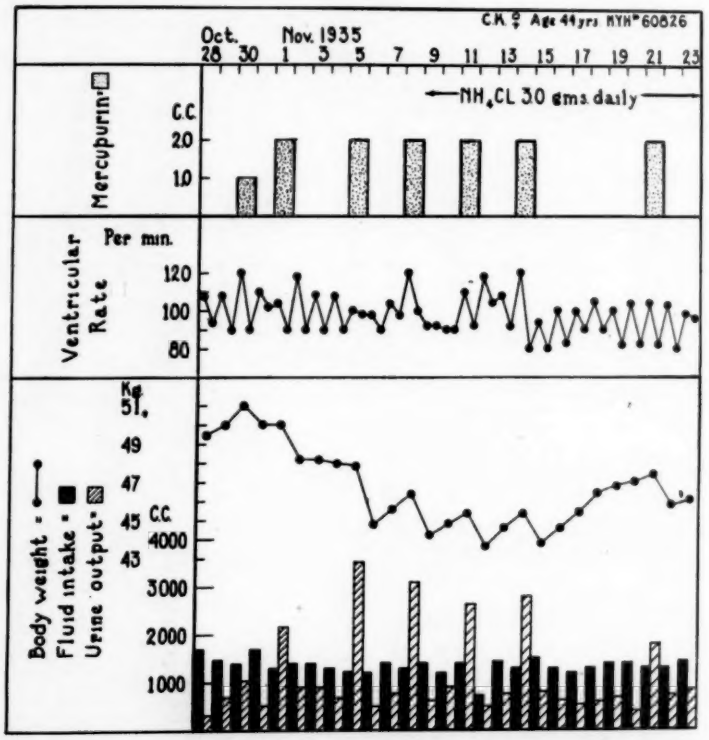

Fig. 7.—In this figure is recorded the diuretic effect of mercupurin in the case of C. K., Case No. 46, suffering from cirrhosis of the liver. The results of the first four injections may be compared with the last three in the period when ammonium chloride was being given.

dence of excess fluid, and that the largest effects occurred for the most part in patients in whom there were physical signs of massive accumulations of fluid. In short, it appeared that the amount of the diuresis was roughly directly proportional to the amount of excess fluid which was available for mobilization.

In 16 patients observations were made both with and without the simultaneous administration of ammonium chloride. It seemed possible in these to make an estimate of its influence on the diuretic effect of mercupurin. This analysis is, of course, open to the criticism that

the status of the patient when ammonium chloride was being given could not with certainty be said to be, and probably would not be, the same as when this drug was not given. Moreover, we have already directed attention to unexplained variation in the diuresis from time to time in the same patient. Nevertheless, in the case of 13 patients ammonium chloride appeared to augment the effect of mercupurin; on the other hand, in three other patients more marked diuresis occurred without the use of ammonium chloride. Most of the patients who gave consistently poor responses did not receive, for one reason or another, ammonium chloride. In the case of two patients who received urea daily for some time, the effect of mercupurin was greater while urea was being given than was the case before or after. In two other cases, however, the administration of urea failed to augment the diuretic effect of mercupurin.

Toxic effects were observed in only 3 of the 66 patients concerned in this analysis. On two occasions Mrs. P. A., Case No. 40, complained of nausea on the day of injection, and on two other occasions she experienced abdominal cramps, mild diarrhea, and slight acceleration of the pulse. It was observed that on each of these occasions there was diuresis of over 4,000 c.c. The physiological strain of excreting so large a volume of urine by a chronically ill patient may, however, account for these symptoms. The second patient possibly exhibiting toxic effects was Miss E. C., Case No. 39. This patient, a girl fourteen years of age, weighed, when free of excess fluid, only 29.0 kgs. She received 43 injections of mercupurin, usually 1.0 c.c. and occasionally 1.5 c.c., without untoward effects. On two occasions when 2.0 c.c. were given she experienced severe nausea on the day of injection. In view of her very small size the reaction occurred probably because the amount of mercupurin was too large. The third patient in whom the question of toxic effects arose was Mr. C. K., Case No. 55. Following two of the six injections which were given he experienced moderate diarrhea not associated with any other unpleasant symptoms. With these exceptions, however, no undesirable effect of mercupurin was observed in any of the 66 patients, many of whom received a large number of injections. Repeated examinations of the urine did not reveal evidence of renal irritation. The relatively low toxicity of mercupurin is well illustrated in the case of Mr. M. W., Case No. 11, who received three doses of 2.0 c.c. each without marked diuretic effect. He was then given 4.0 c.c. on three occasions. Two other patients, Mr. M. K., Case No. 8, and Mr. A. W., Case No. 47, also were given 3.0 c.c. on two occasions. On the occasions mentioned these larger amounts induced more marked diuresis without giving rise to undesirable toxic effects.

The drug was given to two patients in the nephrotic stage of chronic glomerular nephritis. In them there was observed no evidence of toxic effect on the kidney. Mrs. K. O. (Case No. 55, Figs. 1 and 2), a thirty-

eight-year-old woman, who had exhibited massive edema for one year, received 9 injections in a period of sixty-one days. Excellent diuresis resulted, associated with loss of 19.6 kg. in body weight. Mr. C. K. (Case No. 55, Figs. 1 and 2), a fifty-four-year-old man, who had suffered from massive edema for three years, and who was known to have had marked albuminuria during this time, received 6 injections in a period of thirty-two days. The urea clearance was 75 per cent of normal. Only moderate diuresis occurred. It was not effective in reducing the body weight because fluid reaccumulated during the intervals between injection. Examination of the urine of these two patients every two to three days did not show evidence of renal irritation and subsequent observation did not reveal evidence of decrease in renal function.

Venous thromboses and sloughs at the site of injection were not observed. In 5 patients the escape of appreciable amounts of mercupurin into the subcutaneous tissues occurred during injection. In each instance there was erythema, localized edema, and burning pain about the area. These persisted for one to two hours and disappeared. Further reaction did not ensue, however, in any case.

SUMMARY

Four hundred thirty-eight injections of the mercurial diuretic mercupurin were given to 66 patients who presented physical signs of excess fluid in the tissues. Fifty-two patients suffered from heart failure of the congestive type, nine from cirrhosis of the liver exhibiting ascites, two from the nephrotic stage of chronic glomerular nephritis, one from hydrothorax and ascites of unknown etiology, one from tuberculosis of the peritoneum exhibiting ascites, and one from carcinomatosis of the pleura and peritoneum with hydrothorax and ascites. Each patient received from 1 to 45 injections; 2.0 c.c. was the dose usually given.

The results of 286 injections given to 57 patients appeared to represent the diuretic effect of mercupurin uninfluenced by other factors. A statistical analysis was made of these data (Figs. 1 and 2).

Mercupurin appears to be an excellent diuretic drug. It is our impression that it is at least equal and possibly superior to salyrgan in this respect. The diuretic effect varied between 200 c.c. and 5,900 c.c. but was most commonly between 1,000 c.c. and 2,000 c.c. Analyzed in another fashion, the urinary output was increased as much as nineteen times, but most frequently the increase did not exceed five times. These general statements may also be made: it appears to be equally effective irrespective of the etiological types of heart disease; the magnitude of the diuresis appeared to be roughly proportional to the amount of excess fluid stored within the tissues; ammonium chloride appears to enhance its diuretic effect; diuresis in patients suffering from cirrhosis of the liver exhibiting ascites appears to be less striking, al-

though the drug was frequently effective in preventing the recurrence of ascites; good results were obtained consistently in patients suffering from chronic constrictive pericarditis.

Effects which might have been construed as toxic occurred in only 3 patients, although the toxicity of mercupurin is open to question in two of these instances and was inconsequential in the third. On the other hand, mercupurin has the definite advantage that thrombosis or slough did not occur at the site of injection. It is our opinion that of the known mercurial diuretics, mercupurin is to be preferred when it is desired to mobilize fluid.

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EXTRACARDIAC DETERMINANTS OF THE SITE AND RADIATION OF PAIN IN ANGINA PECTORIS WITH SPECIAL REFERENCE TO SHOULDER PAIN*

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A PAINFUL left shoulder is commonly encountered in patients with angina pectoris. Edeiken and Wolferth[1] have recently again called attention to this association. We refer not to the usual radiation of the substernal pain to the left shoulder and left arm, but rather to a continuous intractable pain in the shoulder, which is aggravated by movement of the shoulder, but not by walking, and which prevents sleep because the patient is unable to bear his weight on the joint. The shoulder is tender to touch, and there is, as a rule, sharp limitation of motion on abduction and external rotation. The clinical picture of these painful shoulders resembles that of so-called subdeltoid bursitis, or periarthritis of the shoulder. Roentgen study rarely reveals calcification in the supraspinatus tendon. The condition is very persistent, and usually the pain is out of proportion to the demonstrable lesion in the shoulder.

The association of such painful shoulders with coronary artery disease and angina pectoris is too frequent to be accidental. The overwhelming preponderance of left-sided shoulder pain in patients with angina pectoris is significant. Of our 21 cases 16 were left-sided, and of Edeiken and Wolferth's 14 cases all but two were left-sided. Orthopedists, on the other hand, who see the general run of painful shoulders, report that the majority are right-sided.[2] Did such disability arise from traumatic causes alone, one would expect preponderant right-sided symptomatology, for most people are right-handed. Still more significant is the observation that patients with radiation of the anginal pain to the right shoulder and right arm may subsequently develop right-sided shoulder pain. Edeiken and Wolferth as well as Howard[3] report such cases.

Shoulder pain in patients with angina pectoris may give rise to varied clinical pictures. Most striking are patients who have been conscious of a mild disability and pain in the left shoulder, and who within a day or two following a thrombosis of a coronary artery develop severe, even agonizing, continuous pain in the left shoulder resembling that of a severe periarthritis. The development of such shoulder pain within a week or two after an atypical attack of upper abdominal or chest pain, the diagnosis of which is in doubt, may give the first clue that a cardiac infarction was the cause of the attack.

*From the Medical Service (Dr. George Baehr) Mount Sinai Hospital.
Read before The American Heart Association, section on cardiac disorders, June 8, 1937, at Atlantic City, N. J.

More often the association of left shoulder pain with the anginal syndrome is less dramatic. There are patients in whom the shoulder pain may antedate or may follow the coronary occlusion by many weeks or months, or even years. We have observed a man who had episodes of severe left shoulder pain at the ages of sixty-seven and sixty-nine years, who at the age of seventy-one suffered a coronary thrombosis, without having had preceding anginal symptoms; and who finally at the age of seventy-seven, one month after an attack of acute left ventricular failure, had a third severe attack of left shoulder pain. Not uncommonly there is an intensification of the shoulder disability whenever there is an aggravation of the cardiac condition.

Left shoulder pain is uncommon in forms of heart disease other than that due to coronary artery sclerosis, but we have seen it in a man with the anginal syndrome associated with calcific aortic stenosis, as well as in another patient following paroxysms of auricular fibrillation.

Severe Shoulder Pain Following Coronary Thrombosis

CASE 1.—A. G., a grocer, at the age of forty-seven years, had a sudden attack of constricting pain in the left chest which radiated to the left shoulder and lasted for a few minutes. Following this he had classical angina pectoris on effort. A year later, at the age of forty-eight he had severe attacks of anginal pain. Five days after an attack, which lasted twenty hours, he was admitted to Mount Sinai Hospital. The electrocardiogram on admission showed an abnormal R-T transition and a negative T-wave in Lead I which in five days changed into a typical coronary T-wave. Four days after admission he complained of precordial pressure, with radiation of pain to the left arm on the slightest movement in bed. Several days later he experienced a particularly severe attack of pain referred to the left arm and to the left side of the trunk and with this was unable to move the left shoulder and the fourth and fifth fingers of the left hand. The electrocardiogram revealed no further change. From this time on there were progressive pain and limitation of motion of the left shoulder. The pain was so severe that it required hypodermic medication with morphine. The arm could not be raised passively. Abduction and external rotation caused severe pain. The condition very slowly receded. At the time of discharge, three and one-half months later, there still was incomplete mobility of the left shoulder and distinct atrophy of the left forearm. He was readmitted two months later. Movements of the shoulder caused pain and a creaking could be felt in the joint. There was atrophy of the muscles of the left arm and the forearm. There was hyperalgesia of the left forearm and of the chest. Five months later the shoulder pain persisted and the electrocardiogram at this time showed low voltage and slurring of the QRS in Lead I. The T-wave in Lead I was upright and was partially inverted in Lead III. (He was receiving digitalis at this time.)

Illustrating Right-Sided Shoulder Pain With Right-Sided Radiation of Angina

CASE 2.—P. F., a man fifty years of age, had had attacks of acute febrile polyarthritis at the ages of twenty-four and forty-one. He had no knowledge of an accompanying heart lesion. Beginning about Aug. 15, 1936, walking induced pain to the right of the sternum, which radiated to the right shoulder and which was associated with some difficulty in breathing. The symptoms compelled him to halt and were relieved by nitroglycerine. Excitement induced similar pain. On about Nov. 1, 1936, he developed continuous pain with limitation of motion in the right shoulder. This

pain was not induced or intensified by exertion and lasted about a week. Examination on Dec. 17, 1936, revealed a pasty complexioned man. The lungs were clear. Movements of both shoulders were free and painless. Fluoroscopy revealed slight enlargement of the left ventricle and of the left auricle. The first heart sound was dull. There was a systolic murmur at the apex, transmitted a short distance to the axilla. Blood pressure was 110 systolic and 80 diastolic. The electrocardiogram showed slurring of the QRS in all leads, Q-waves in Leads II and III, and a negative T-wave in Lead III. The QRS interval measured 0.12 second. The patient had an old inactive rheumatic mitral insufficiency, as well as an old infarction of the posterior aspect of the left ventricle.

This case illustrates not alone right shoulder pain with right-sided anginal radiation, but suggests that the onset of the shoulder pain marked the occurrence of a coronary thrombosis.

Intensification of Shoulder Pain by Intercurrent Coronary Thrombosis

CASE 3.—M. S., a man aged forty-nine years, had known of glycosuria since early in 1934. Beginning in March, 1933, and persisting for two years he had had pain in the right upper interscapular region, which radiated to the right lower anterior chest. This pain occurred only while he was resting in bed, was relieved by moving about and was not induced by exertion. In December, 1934, he complained of increasing tiredness and of some pain in the posterior aspect of the left shoulder which was intensified by movement of that joint. On March 15, 1935, he suffered an attack of right lower anterior chest pain which radiated to the angle of the right scapula and which lasted two days. With this there was intermittent cramping epigastric pain. Examination on March 18, 1935, revealed a man looking rather old for his years. The lungs were clear. Fluoroscopy revealed a heart of normal size and configuration. The aorta was elongated and dense. The heart sounds were of good quality. There were no murmurs. Blood pressure was 135 systolic and 85 diastolic. The electrocardiogram was normal in the conventional leads, but there was a very deep T-wave in Lead IV. He stayed in bed for two months. During this time he complained of a rather constant pain over the lower right ribs, both anteriorly and posteriorly. The pain was aggravated by movement of the trunk, but not by walking. Examination on May 13, 1935, revealed free movements of the spine and no bands of hyperesthesia. There was tenderness over the lower anterior ribs on the right side. The electrocardiogram now showed a small diphasic T-wave in Lead IV. In August, 1935, the right shoulder was very painful for a week. This cleared up and pain developed in the left shoulder which persisted for four months. In December, 1936, he had an attack of precordial pain in the region of the apex, which lasted one hour, compelling him to rest in bed for two weeks. There was no radiation of pain during the attack, but following the attack the left shoulder pain, which by this time had become minimal, became intensified and limitation of motion of the shoulder joint appeared. The electrocardiogram on Jan. 15, 1937, again revealed a deep T-wave in Lead IV.

This case illustrates intensification of shoulder pain by intercurrent attacks of coronary thrombosis as well as a shift from the right shoulder to the left shoulder as the anginal pain moved from the right of the sternum to the region of the apex.

Relief of Anginal Pain by Pressure on the Brachial Plexus

CASE 4.—S. R., a man aged fifty-seven years, had had typical angina pectoris since 1929. On Oct. 6, 1935, he had a nocturnal attack of severe cramping pain in both arms above the elbows, which lasted for ten minutes. There was no associated chest pain. Following this he developed distressing pain in the left shoulder which persisted for two months. There was no further angina on effort, but the shoulder was constantly troublesome and he was unable to use the left arm. Examination revealed moderate limitation of abduction and external rotation of the left shoulder.

Movements were limited by muscle spasm and severe pain. Libman's maneuver for the relief of this shoulder pain was attempted. A point was found over the left brachial plexus, pressure on which caused severe pain which radiated to the left shoulder and down the left arm. Strong pressure was exerted on this spot for about two minutes until the whole left arm became numb. This pressure caused agonizing pain, so that the patient perspired freely. Immediately after the cessation of the pressure, the pain in the shoulder disappeared and all movements of the arm and the shoulder were absolutely free. Complete relief lasted for twenty-four hours. Pain recurred then in milder degree and was relieved by ten diathermy treatments.

CASE 5.—I. R., at the age of forty-four years, in 1932, suffered a coronary thrombosis after having had angina pectoris on effort for two months. During the cardiac infarction there was sticking pain in both forearms. Following this he had anginal pain on effort without radiation to the shoulders or arms. When last seen in May, 1937, he stated that for two months he had felt pain in the right wrist on walking five blocks, as well as on change of weather. Six weeks after the onset of these symptoms he was awakened at night with severe pain in the right shoulder. He was unable to lie on his back. This pain persisted to the day of his examination ten days later. Abduction of the arm was limited to 90 degrees and there was pain on external rotation. Pressure on the right brachial plexus caused severe pain without radiation to the shoulder or arm. Strong pressure was thus exerted for one minute. Following this the shoulder pain was gone and movements of the shoulder joint were free. In putting on his coat the patient was surprised at the freedom from pain. A few moments before his wife had had to help him take off his coat because of the crippling pain in the shoulder. The cardiac status and electrocardiogram on the occasion of this examination were unchanged.

This case again illustrates right shoulder pain with right-sided anginal radiation, as well as successful relief by the Libman maneuver.

Painful Left Shoulder in a Patient With Angina Pectoris Due to Calcific Aortic Stenosis

CASE 6.—W. F., a man aged fifty-nine years, had had articular rheumatism as a child, and had known of a heart lesion since the age of twenty years. He was first observed at the age of fifty when he complained of dyspnea on climbing stairs and of transient attacks of faintness. Examination revealed a classical aortic stenosis and insufficiency with little cardiac enlargement. At the age of fifty-six he began to have a burning pressure under the sternum when walking after meals, sufficiently severe to compel him to stand still. This gradually became worse so that after three more years he could hardly walk one block. At the age of fifty-nine his left shoulder became painful. The pain was continuous and was intensified by abduction of the left arm. Examination two months after the onset of the shoulder pain revealed great enlargement of the left ventricle, moderate enlargement of the right ventricle and slight left auricular enlargement. There was a systolic thrill and murmur at the aortic area, as well as a diastolic murmur which latter was transmitted to the apex. Blood pressure was 120 systolic, 85 diastolic. The electrocardiogram which had been normal nine years previously showed inversion of T_1, diphasic T_2 and T_4, and a very small initial downward deflection in Lead IV. The left shoulder, particularly its outer aspect, was tender and there was marked limitation of motion on abduction and external rotation. Nine days after this examination the patient died suddenly, six hours after an attack of severe precordial pain.

Painful Left Shoulder in a Patient With Paroxysmal Auricular Fibrillation and No Demonstrable Organic Heart Lesion

CASE 7.—P. F., a man aged forty-two, on Dec. 1, 1936, had a sudden attack of palpitation and dyspnea which lasted about an hour. He noted a rapid irregular beating of his heart. On April 8, 1937, he had a second attack which lasted two

and one-half hours. An electrocardiogram revealed auricular fibrillation with rapid ventricular rate and many extrasystoles. A third attack lasting two hours occurred on April 18, 1937. Ever since the first attack the left shoulder has been slightly painful, although movements of the shoulder were free. He observed that the shoulder pain on each occasion was intensified for about an hour after an attack of rapid palpitation. Examination on April 23, 1937, at a time when there was normal sinus rhythm was completely negative. No organic heart lesion could be demonstrated, the blood pressure was 120 systolic and 80 diastolic. The electrocardiogram was normal. There was no evidence of hyperthyroidism. The left shoulder was not tender and all movements were free and painless.

DISCUSSION

It is most important to distinguish this shoulder pain from the pain of anginal radiation. The patient can clearly differentiate the two. The shoulder pain is continuous, often intensified at night when the patient lies on the shoulder, aggravated by movements of the arm, but not by general body exercise, and there is limitation of abduction and external rotation of the arm. When angina and shoulder pain coexist, and when the shoulder pain is intensified by the angina on effort, nitroglycerine relieves the chest pain but not the shoulder pain. Many patients are kept in bed for weeks by their physicians in the erroneous belief that the persistent shoulder pain signalizes a progressive cardiac lesion. Although these painful shoulders are often initiated by an acute cardiac episode, they may persist for months without further progress of the heart lesion, and often yield to appropriate physiotherapeutic measures, in particular diathermy. At times they are miraculously cured by the maneuver described by Libman[4]—strong, prolonged pressure for one or two minutes on a sensitive point over the corresponding brachial plexus.

The mechanism of shoulder pain in patients with coronary artery disease remains obscure. The syndrome has been described by a number of observers. R. Schmidt[5] pointed out that in many patients with angina pectoris there are permanent sensitive spots, particularly the left brachial plexus. There is often tenderness along the spinal nerve roots from C7 to D4. Trophic disturbances such as herpes zoster, and hyperhydrosis have been observed in this distribution. There are arthralgias of the left shoulder and rheumatic myalgias in the area of trophic disturbance, as well as paresthesias of the left upper extremity which often persist between attacks. To explain all of these phenomena Schmidt assumed a neuralgic or neuritic condition of the cardio-aortic plexus, and postulated that the anginal attack just added a peak to a permanent state of excitation.

Libman has been interested in this phenomenon for years and in 1927[6] described a patient with angina pectoris and severe left shoulder pain, which radiated down to the fingers. The patient also had a cervical rib, and had had tingling and weakness of the hand, but no pain for

years. Libman concluded that the angina pectoris or a neuralgic condition of the cardiac plexus had sensitized the cervical nerves and had converted the tingling and weakness into severe pain. In 1935[7] he pointed out that a subacromial bursitis will begin to give pain shortly after a coronary thrombosis has occurred. He suggested that the frequent coexistence of shoulder pain and angina pectoris was determined by the fact that they were both caused by the same metabolic disturbance.

Lian[8] in discussing angina pectoris complicating left thoracobrachial neuralgias expresses the belief that the cervical neuralgia is the result of repeated "nerve shocks" caused by the frequent anginal seizures. The brachial neuralgia, in turn, may cause an ankylosis of the left shoulder. Lian believes that the reverse process can take place; that pure brachial neuralgias can give typical anginal radiations, and that in such cases a retrograde radiation takes place.

Edeiken and Wolferth suggest an analogy between shoulder pain and causalgia and that the sympathetic nerves may be concerned in the production of the pain. Interesting in this connection is a report by Kwan[9] of a patient with severe causalgia of the left arm following a bullet wound that had shattered the clavicle. At operation the brachial plexus was found imbedded in scar tissue and the axillary artery was obliterated. Dissection of the scar tissue and excision of several inches of axillary artery brought no relief. The pain ceased promptly following cervicothoracic ganglionectomy.

There is no satisfactory explanation of the manifestations of shoulder pain in patients with angina pectoris. A large group of associated and apparently related phenomena must be considered together in an attempt to gain an understanding of the mechanism involved. Shoulder pain occurs with exceptional frequency in patients with angina pectoris. With left-sided anginal radiation it is almost always the left shoulder that is involved. When the right shoulder is affected there is almost always right-sided anginal radiation. Other disturbances in the arm are often encountered, even in the absence of shoulder pain. One of the most striking is weakness or lameness of the left arm. This is a very common complaint of patients with left-sided anginal radiation. Recently we saw a man who had lost his anginal pain after having suffered a coronary thrombosis with right-sided radiation, but who was unable to work because of weakness of the right arm. Not uncommonly one sees inverse radiation in angina pectoris, the pain beginning in the fingers and traveling up the arm to the precordium. At times in such cases this inverse anginal seizure is provoked by use of the arm or by touching a cold object. Frequently, too, a patient will be able to walk quite freely without pain, but if he carries a light overcoat or brief case in the left arm he is stopped by an anginal attack after walking a short distance. Yet he can carry heavier articles in the right hand without distress.

At times lameness of the left arm when carrying light objects may be the first and only symptom of angina pectoris, the classical picture appearing months or years later.

Herpes zoster in skin areas corresponding to the distribution of the pain has been repeatedly described in patients with angina pectoris.[10] Cases of localized sweating in the shoulder and arm in anginal patients have been recorded.[11, 12] Hatiegan and Liviu[13] observed five patients who during their anginal attacks had painful contractures of the left upper extremity, especially of the fingers of the left hand. Bard[14] studied a man, aged thirty-three, whose left middle finger "went dead" during anginal seizures. Between anginal attacks the third toe of the left foot repeatedly became pale and cold. The patient died suddenly in an anginal seizure.

A more striking illustration of the relationship between the brachial plexus and referred precordial pain is found in the following case of Aronowitsch.[15] A man, aged twenty-nine, had a neuroma giving rise to a severe neuralgia in the stump of his left arm that had been amputated at the lower third. At operation two neuromas were extirpated. Four days later severe pain in the left arm appeared. This was soon followed by air hunger and a feeling as though the heart had stopped beating. In addition there were crises of pain in the precordium, neck, and left shoulder as well as precordial oppression. Examination of the heart revealed no abnormalities. After drainage of a hematoma that had formed in the stump, the pain and the anginal seizures slowly disappeared.

Much has been written about pain in the left chest and shoulder girdle caused by arthritis of the cervical spine. Hanflig[16] observed that although the shoulder joint was painful its movements were not limited and there was no spasticity of the shoulder muscles. In patients with narrowing of the lower cervical intervertebral discs pain in the shoulders, arms, and precordium may occur, and with this there is often inability to raise the arm as in brushing the hair. But even in such patients passive movements of the shoulder are free.[17] Shoulder pain associated with angina pectoris is characterized by marked limitation of motion of the shoulder and spacticity of the muscles around the shoulder joint. This suggests that different mechanisms are involved in the two conditions.

Our first thought was that there was an independent affection of the shoulder, and that the radiation of anginal pain down the same sensitized pathway merely intensified the pain due to the local lesion. Carnett[18] believes that shoulder reference of pain and tenderness in biliary colic as well as in angina pectoris occurs only as an aggravation of a neuralgia, due to some extraneous cause. It is interesting that shoulder pain of the type seen in angina pectoris is not observed in patients with chronic gall bladder disease, although referred pain to the right shoulder is

very common. The distribution of anginal pain in patients with spondylitis, or with peptic ulcer or gall bladder disease, as will be described below, also suggests that sensitization of a dermatome by another disease process may determine the spread of anginal pain and increase its intensity. However, the weight of evidence points to a primary sensitization of the brachial plexus by afferent pain impulses from the heart.

Our own observations together with those culled from the literature reveal the frequent occurrence of sensory and trophic disturbances in the arm and shoulder which have been the seat of radiation of pain in anginal seizures. These neurogenic disturbances of the upper extremity differ in character and mechanism from the usual type of referred pain. The disorder persists long after the anginal attack, although it is usually intensified by recurrent attacks; there is no hyperesthesia of the skin in the corresponding dermatomes; the brachial plexus and some of the nerves derived from it are tender on pressure. The shoulder joint, which is so often the seat of a very painful affection, is innervated by the fifth and sixth cervical nerves, whereas cardiac afferent impulses enter the dorsal ganglia in the first five dorsal segments, but not at higher levels. Firm pressure on the homolateral brachial plexus evokes intense pain referred to the shoulder, and prolonged pressure may bring about instantaneous relief of the pain and limitation of motion of the affected shoulder (Libman).

Recent work on the electrophysiology of nerves has shown that periodic painful impulses are capable of building up intense activity in the central neurone and may thus give rise to constant pain. One would have to suppose that periodic cardiac afferent impulses are in this manner conducted to higher levels in the spinal cord, and that there a summation of their effects gives rise to continuous pain in the brachial distribution. The suggestion of Schmidt and Lian that a neuralgia of the cardio-aortic plexus gives rise to a brachial neuralgia explains nothing and is but a phrase. If some such mechanism obtains, then alcohol block of the first five thoracic ganglia on the affected side should, by eliminating the cardiac afferent impulses, lead to rapid subsidence of the shoulder and arm affection. We have not yet had opportunity to test this in a patient. According to this concept, too, shoulder pain occurring before manifestations of angina pectoris might in certain cases be evidence of cardiac afferent impulses of insufficient intensity to produce the anginal syndrome. This is in accord with Schmidt's observation that tenderness of the brachial plexus on the left side may antedate the appearance of the symptoms of angina pectoris.

The location and radiation of pain in patients with angina pectoris presents other puzzling phenomena. Years ago Mackenzie[19] drew attention to the fact that if a patient with angina pectoris had an abscessed tooth the anginal pain would radiate to that tooth.

The usual radiation of the pain of angina pectoris is along the course of C8 and D1 and D2, involving the precordium, left shoulder, and upper extremity. According to the theory of referred pain, if the sensory stimuli from the heart make irritable spinal segments other than those at their level of entry into the spinal cord, corresponding dermatomes are affected, the pain spreads (or radiates) and may be felt in the neck, face, scalp, abdomen, and even in the thigh. If a second disease process, e.g., an abscessed tooth, sensitizes a spinal segment at a level distant from the one corresponding to the heart, this distant area may be the sole seat of pain induced by and reflected from the heart. If the distant spinal segment is less highly sensitized, pain may be felt first in the dermatome corresponding to the heart, and secondarily in the distant area. Thus there may be radiation of pain to distant areas, with intervening silent zones.

The following cases illustrate these phenomena:

P. K., a woman aged forty-nine years, had known of glycosuria and hypertension for seven years. For twelve years weather changes had produced moderate tearing pains of all of her extremities. Since the age of forty-one, hurrying or going up stairs induced pain in the suboccipital area, which radiated to the scalp and to the thoracic and lumbar spine. The pain was severe and cutting in nature and associated with some difficulty in breathing. It compelled her to rest. The pain was relieved by strong pressure of the hand exerted over the back of the neck. In January, 1937, at the age of forty-nine, she had severe pain throughout the body as though it were "broken" and the right arm and neck were very painful. Some hours later the pain became more severe and radiated from the neck down the right arm. There was no chest pain. The blood pressure dropped from its usual level of 230 to 150 systolic, and the temperature rose to 102.5° F. and remained elevated for several days. Examination a few days later revealed as a striking finding marked tenderness of the right shoulder and inability of abduction and external rotation because of severe pain. The heart was enlarged to the left. The heart sounds were of good quality. Blood pressure was 200/90. She was reexamined five weeks after her attack. Fluoroscopy revealed moderate enlargement of the left ventricle. Blood pressure was 175 systolic and 75 diastolic. The electrocardiogram revealed a large Q-wave in Lead I. The T-waves were low and the R-T segment depressed in all leads. The shoulder pain and tenderness had disappeared and motion of the arms was free. There was no abnormality of the spine.

We believe that in this case there had been a mild spondylitis for twelve years which determined the radiation of the pain. The case, too, illustrates right-sided radiation with right-sided shoulder pain.

S. H., a woman aged fifty-nine years, had known of hypertension for one year. Ever since the age of thirty years she had had attacks of "lumbago," characterized by severe pain in the lumbosacral area, which would last for several days and confine her to bed. She had had her last attack at the age of fifty-four. In her fifty-eighth year she began to complain of lumbosacral pain which would radiate up the dorsal spine and would be associated with a sense of choking. This pain would come when she walked a few blocks quickly and would compel her to rest. She said that the pain would be unbearable if it lasted more than a few moments. Similar lumbosacral pain was induced by excitement. She was examined in 1937 at the age of fifty-nine. She was rather stout, with a pendulous abdomen. There were scattered

wheezes throughout both lungs. Fluoroscopy revealed slight enlargement of the left ventricle. The first heart sound was feeble. There were no murmurs. Blood pressure was 200 systolic and 100 diastolic. The electrocardiogram revealed very low T-waves in all leads, particularly in Lead I. The urine showed much sugar. There was no evidence of local disease or tenderness in the lower spine or in the sacroiliac region. She was given a reduction diet, as well as a corset to support her abdomen. She lost nineteen pounds in two months. She was able to walk much more freely and her attacks occurred less frequently. However, at the end of this period her niece died and on this occasion the patient had an attack of severe pain in the sacrum, radiating to the spine associated with a sense of choking which lasted only a few minutes.

In this case the anginal pain radiated to the sensitized lumbosacral spine.

Harlow Brooks[20] described a man who had had chronic appendicitis for years and who then developed angina pectoris. Effort regularly provoked pain in the right lower quadrant of the abdomen, which radiated to the sternum and down the left arm. A man with renal calculus regularly felt on exertion pain in the region of the affected kidney, associated with substernal oppression.[21] In another man with long-standing occipital neuralgia the anginal pain radiated to the back of the head.[22]

Well known are cases in which the pain of coronary thrombosis is referred to the epigastrium and is associated with vomiting, giving rise to the clinical picture of perforated peptic ulcer or acute cholecystitis. Ulcers of the stomach, or peptic ulcer of the esophagus may cause substernal pain that may radiate to the region of the cardiac apex and to the left shoulder. Such pain bears a definite relationship to the ingestion of food. The usual site of pain in peptic ulcer is in the epigastrium. It may radiate to the entire abdomen and to the lower anterior chest.

When a patient with a peptic ulcer develops coronary artery disease, the ulcer pain may follow the distribution of the anginal pain. This is exemplified by the case of a man, aged fifty, who had nocturnal epigastric pain that radiated to both axillae and down the inner aspects of both arms to the elbows. The pain was relieved by a warm drink. Identical pain occurred an hour after meals. The same pain, however, was induced by walking a few blocks and compelled him to stop. Following treatment in the hospital, the spontaneous pains after meals disappeared, but walking a few blocks produced substernal pressure and pain in the right shoulder compelling him to halt. Five weeks after the onset of his symptoms he had a hematemesis and blood in his stools. X-ray studies showed the presence of a duodenal ulcer. The electrocardiogram showed left axis deviation, a sharply negative T-wave in Lead I and an abnormal R-T segment in Lead II. This patient had both angina pectoris and a duodenal ulcer, and the ulcer pain radiated down the sensitized cardiac pathways. Treatment induced a remission of the ulcer pain, but the angina on effort persisted.

L. D., a male, at the age of thirty-eight had had, for a period of four weeks, lower sternal pressure shortly after meals and lasting half an hour, associated with heaviness of both arms and difficulty in raising the shoulders. Such pain occurred frequently at night and lasted one to two hours. Roentgen studies of the stomach at that time were said to be negative. The symptoms remitted spontaneously and he remained in good health until the age of forty-nine, when on Nov. 16, 1936, one hour after lunch, he experienced sudden lower sternal pressure with pain radiating up both sides of the face, lasting about an hour. There was no sweating. He continued at work and two days later there was a recurrence of similar pain radiating to the face, which lasted all night. During the following two and a half weeks this pain with facial radiation appeared regularly half an hour after meals. He entered Mount Sinai Hospital on Dec. 6, 1936, at which time the pain was not definitely related to meals and lasted for hours on end. It was situated over the lower sternum and radiated to the face. The patient was given a strict Sippy diet and milk drip therapy and the pain ceased. An electrocardiogram taken at this time revealed evidence of a recent cardiac infarction. Roentgen study of the gastrointestinal tract showed a gastric ulcer. Following his discharge from the hospital he noted fatigue after walking half a block, compelling him to slow his pace. He never felt actual chest pain or pressure on exertion. When last examined in February, 1937, he had no abdominal tenderness. Fluoroscopy revealed some enlargement of the left ventricle and left auricle. The first heart sound was loud; there was a systolic murmur at the apex. The blood pressure was 115 systolic and 70 diastolic. The electrocardiogram showed a negative T-wave in Lead I, an absent initial downward deflection and an upright T-wave in Lead IV.

This man had had a gastric ulcer eleven years previously. In November, 1936, he had a coronary thrombosis marked by pressure over the lower sternum and radiation of pain to the face. Shortly thereafter he developed typical periodic ulcer pain, with the same radiation as the cardiac pain, which was relieved by a Sippy regimen. The ulcer pain followed the pattern previously laid down by the anginal radiation.

At times ulcer pains may have a typical anginal radiation in the absence of objective evidence of coronary artery disease and of angina on effort. In such cases one should suspect the presence of a latent coronary sclerosis. Illustrative of this is a man, aged fifty-four, who six years previous for two weeks had dull pain in the left parasternal region occurring about 3 P.M. and lasting about one-half hour, and relieved by alkali and by milk. The pain was unrelated to exertion. Three years later there was a recurrence of similar symptoms for a brief period. He was then well until a month before his examination, when he began to notice left parasternal pain, which radiated to the epigastrium and to the left shoulder. The pain awakened him almost every night. It began in the epigastrium and radiated to the precordium and left shoulder and was relieved by bicarbonate of soda. Walking did not produce the pain. Physical examination, in particular of the heart and abdomen, was completely negative. The electrocardiogram was normal. Roentgen study revealed a duodenal ulcer. The symptoms were promptly relieved by a Sippy diet. When seen one and a half

years later, he was symptom free. Examination and electrocardiography of the heart again were normal.

Pain arising in a diseased gall bladder may simulate the pain of angina pectoris, and in such cases it is difficult to determine which of these organs is giving rise to the symptoms. It has been shown experimentally in human subjects that inflation of the common bile duct by means of a rubber balloon may cause pain referred to the precordium.[23] In the presence of a normal heart it is unusual for the pain of gall bladder disease to radiate to the precordium. In patients who have both gall bladder disease and coronary artery disease the pain provoked by the cholecystic disease may radiate to the precordium and left arm. Lian[24] has reported the case of a man with angina pectoris and gall bladder disease in whom pressure over a palpable gall bladder repeatedly provoked anginal crises with radiation down the left arm. We have recently seen a similar case.

B. R., a man aged fifty-six years, had had classical angina pectoris on effort for five years. He has been observed in the cardiac clinic at Mount Sinai Hospital since July, 1933. A study in December, 1934, revealed a heart of normal size and configuration. The electrocardiogram showed the QRS complex slurred in Leads I and IV, the T-wave negative in Lead I, diphasic in Lead IV, and an absent initial downward deflection in Lead IV. Roentgen study of the gall bladder with dye was normal. He entered the hospital in May, 1936, because of right upper quadrant pain. One and one-half months previously he had had an attack of such pain which had lasted two days, for which he had received a hypodermic injection. Twelve days before admission colicky right upper quadrant pain recurred and persisted to the day of his entry to the hospital. Examination at this time showed a temperature of 101° F., a white cell count of 18,900 with 76 per cent of polynuclear leukocytes. The patient was hypersensitive. The first heart sound was feeble. The pulmonic second sound was accentuated. The blood pressure was 150 systolic and 100 diastolic. There was marked tenderness in the right upper quadrant and the liver could be felt extending three finger-breadths below the costal margin. Pressure in the right upper quadrant, particularly in the anterior axillary line, caused pain beneath the examining finger, as well as pain to the left of the sternum and difficulty in breathing. There was no trapezius or brachial plexus tenderness on either side. In the course of ten days the temperature and blood count returned to normal. The blood pressure dropped to 115/75, and the tenderness in the right upper quadrant gradually abated. On about the eighth day pressure in the right upper quadrant caused no local pain, but did cause sharp pain referred to the precordium. The electrocardiogram revealed a small Q-wave and a flat T-wave in Lead T, and an absent initial downward deflection and a diphasic T-wave in Lead IV. The gall bladder was not visualized on x-ray film after the administration of dye.

In this case a man who had had coronary artery disease for some years developed an acute cholecystitis. Pressure over the gall bladder provoked sharp precordial pain.

The interpretation of such cases is not as simple as it seems. When there is unequivocal evidence of coronary artery disease it may be assumed that the pain from the gall bladder radiates down the sensitized

cardiac pathways. But studies of Fitz-Hugh and Wolferth[25] seem to indicate that at times the gall bladder disease may cause injury to the myocardium, giving rise to anginoid pains and T-wave changes in the electrocardiogram, and that after operative cure of the gall bladder condition the precordial pain may completely disappear and the electrocardiogram return to normal. We have seen a patient who seems to fall in this category.

H. G., a man, was first seen in 1932 at the age of forty-one years. In 1930, following a bowel movement he suffered severe cramping pain in the entire abdomen. With this he perspired freely, and had marked palpitation. He recovered quickly and a few weeks later had a similar attack. On both occasions he was able to work the day after the attack. In 1932 he complained that for two months he had been having sharp momentary stabbing pains in the precordium while walking, which compelled him to stop. When he was tired he felt a continuous pressing sensation in the precordium which was aggravated by walking, but this did not compel him to stop whatever he was doing. Examination at that time was negative. He was obese. The heart was not enlarged; the heart sounds were of good quality. The blood pressure was 118 systolic and 80 diastolic. The electrocardiogram was normal. He was seen again in February, 1937. He had had a herniotomy in June, 1936, and two months later had had an attack of lower abdominal cramps, with sharp precordial pain about the apex, and vomiting. He was in bed for one week after this attack. In December, 1936, he was awakened at night by severe sticking apical pain with difficulty in breathing. Deep inspiration reproduced the precordial pain. In February, 1937, he had a similar attack with fever followed by two milder attacks on the following days. The precordial pain was relieved by nitroglycerine. On the third day he became icteric. Physical examination was negative except for moderate jaundice. The heart showed no abnormalities. The electrocardiogram, however, revealed T-waves that were practically flat in the three conventional leads. He was admitted to Mount Sinai Hospital where a cholecystectomy and a common duct exploration were performed. Gravel was found in the common duct. The gall bladder showed a chronic cholecystitis. Recovery was uneventful. He was seen six weeks after the operation. He was completely free from all symptoms. The electrocardiogram was normal; the T-waves again were of normal configuration.

Has this patient both gall bladder disease and coronary artery disease, or were the cardiac pain and the myocardial damage as shown by the electrocardiogram secondary to the gall bladder affection?

SUMMARY

An affection of the shoulder characterized by pain, muscle spasm, and limitation of motion occurs commonly in patients with angina pectoris. With rare exceptions the left shoulder is involved when there is left-sided radiation of anginal pain; the right shoulder when there is right-sided radiation. This shoulder pain is continuous, is not exaggerated by factors that usually induce anginal pain, but is often aggravated by sudden progress of the heart lesion, such as coronary thrombosis or acute left ventricular failure.

Such shoulder pain does not call for bed rest and treatment of the heart, but is relieved by local physiotherapeutic measures. At times the

Libman maneuver—firm pressure on the homolateral brachial plexus—brings about instant relief of this pain and limitation of motion.

The mechanism of this shoulder pain remains obscure. Certain analogies suggest that the radiation of the anginal pain to the shoulder superimposed on a local slightly painful affection of the shoulder may by summation induce this painful disablement. However, the many other trophic and sensory disturbances that may occur in the left upper extremity in patients with angina pectoris, suggest rather that the chief factor lies in some reciprocal relationship between afferent impulses from the heart and sensitization of the neurones whose fibers go to make up the brachial plexus.

The site and radiation of anginal pain may be determined by extracardiac lesions, such as abscesses of the teeth or spondylitis. In such cases the anginal pain may be experienced only or chiefly in the area sensitized by somatic disease.

Conversely in the presence of peptic ulcer or of gall bladder disease the pain arising in the ulcer or in the gall bladder may follow the anginal radiation.

Fitz-Hugh and Wolferth's observation is confirmed that there are patients with gall bladder disease, with reference of the pain to the precordium and T-wave changes in the electrocardiogram, in whom operative removal of the gall bladder is followed by disappearance of precordial pain and a return to normal of the electrocardiogram.

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SIXTEEN YEARS' EXPERIENCE WITH HEART DISEASE IN PREGNANT WOMEN

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THIS is a brief review of sixteen years' experience as cardiologist at the Boston Lying-In Hospital. There were more than 44,000 deliveries, 850 of the patients being classed as cardiacs, during this period.

Angus MacDonald of Edinburgh published a description of 29 pregnant women with severe heart disease in 1878.[1] I will quote a part of his first description. The patient was thirty-four years old, and had mitral stenosis. She had no disability until the seventh month in her first pregnancy when she caught a cold and had congestive heart failure. This was cured by a regime and digitalis and she was delivered successfully at term.

> . . . She felt much better after her confinement, and suckled her child; and her health remained good till she became pregnant for the second time. Towards the middle of this pregnancy she became very markedly anaemic; her breathlessness, palpitation, and general discomfort returned, and her legs became enormously oedematous. About the end of the seventh month there was present general oedema, with cough and orthopnoea. I intended about this time to arrange for a consultation, with the view of deciding upon the propriety or otherwise of inducing premature labour, as Mrs. S. was now unable either to lie down or move herself in bed, so much pulmonary oedema and general anasarca were present. But on the 18th of May, 1872, the patient, being near the end of the eighth month, fell in labour. The delivery was easy. I gave chloroform with some hesitation at first, but it was well borne, though the pulse was exceedingly weak and very irregular. Mrs. S. did not improve much after the completion of labour. The anasarca and the dyspnoeic symptoms continued, and she was scarcely able to take any food. Her condition remained much at a standstill, however, till the morning of the sixth day after her delivery, when she suddenly fell back in bed dead.

Before 1921 somewhat similar cases furnished almost 25 per cent of all the maternal deaths at the Boston Lying-In Hospital. At this time the only convincing modern information on the subject was Sir James MacKenzie's[2] statements (1) that patients with auricular fibrillation did not do well in pregnancy, (2) that when cardiacs died in pregnancy, death was due to congestive heart failure, and (3) that the earliest sign of heart failure was persistent râles at the lung bases.

In the first three years of my service, 72 patients with severely damaged hearts were delivered. Eight died. Twelve of these had severe congestive heart failure as described by MacDonald. Faced with such women in the last trimester of pregnancy, we felt that for any likeli-

Read before The American Heart Association, section on cardiac disorders, at Atlantic City, N. J., June 8, 1937.

hood of lasting relief the uterus must be emptied. Accouchement forcé had already been shown to yield a high death rate in such cases. Eleven of the failing cardiacs were therefore delivered by abdominal hysterotomy. It was found that (1) the patient survived the operation, but 50 per cent died days later; (2) there was no apparent marked amelioration of symptoms directly following emptying the uterus. This method of treating heart failure in pregnancy was, therefore, abandoned, and persistent effort made to relieve the failure before attempting delivery. The results were better, but still 25 per cent of such patients died. For thirteen years emphasis has been placed where it belongs on early classification, selection, and stubborn control of the cardiac in pregnancy.

From the beginning we have used a very simple *classification* based on direct examination of the heart and it has proved to be sound. The patients in the heart clinic fall naturally into three groups:

I. Those who have unmistakable evidence of severe heart damage, either (1) enlargement, or (2) a diastolic murmur, or (3) signs or history of heart failure, or (4) a dangerous disorder of the heart beat.

II. Those who have less evidence of heart damage, for example, doubtful enlargement, a systolic murmur.

III. Those with cardiac neurosis, N.C.A., or other perhaps disabling symptoms, but no evidence of heart damage.

Recognizable heart failure has not been found except among those who could be placed in Group I. Twenty per cent of the Group I cardiacs showed some form of recognizable heart failure during pregnancy. So far as pregnancy is concerned, no woman need be considered a "cardiac" unless she has the criteria for Group I. Of 850 such cardiacs delivered, 781 were considered to have rheumatic heart disease. The remaining 69 fell into small groups that must be considered distinct problems—congenital heart, enlargement with hypertension, cardiovascular syphilis, thyroid heart, blocks and other disorders of the heart beat. The prognosis and the nature of the dangers to be feared differ greatly in these groups.

How can we subdivide the 781 *rheumatic heart disease cases in respect to their prognosis in pregnancy?* A natural subdivision of the Group I cardiacs appeared early in the study and has proved its value, namely, Group I cardiacs who have (1) already developed recognizable heart failure, or (2) a complication in itself dangerous. The only common complication has proved to be auricular fibrillation, and this is surprisingly rare. Only 18 cases have had it either established or as a transient event. The maternal death rate is thirty-three and one-third per cent. Sir James was right, though he did not suspect its rare occurrence. Only one out of seven of all the fatal cases among the cardiacs had auricular fibrillation at any time.

Cardiacs classified as Group Ia when first seen (on a basis of previous congestive heart failure) have had a maternal death rate of 16 per cent.

Cardiacs classified as Group I when first seen have a maternal death rate of 3.5 per cent. Cardiacs classified as Group I who have not developed heart failure and therefore changed their status to Ia during pregnancy have a maternal death rate of 2.3 per cent. Whatever other classification one may like to use, these natural groupings must be respected. These statistics give us something definite to tell our patients and to direct us in their care. They comprise all that is surely known about the prognosis of patients with rheumatic heart disease in pregnancy. It is reckless to try to state the risk for any single case with accuracy. One can only guess a somewhat greater or less risk for the individual within these classes. Minor differences in the degree of heart damage are not directly pertinent to the problem of prognosis in pregnancy. For one illustration: one would expect a higher death rate where aortic regurgitation is added to mitral stenosis than with either valve lesion alone. But the maternal death rate differed only three-tenths of one per cent in patients with mitral stenosis with aortic regurgitation or with both, from the average death rate of all three. Patients with uncomplicated mitral stenosis differ greatly, of course, in their pathological signs and in their ability to exert themselves. But until they have developed auricular fibrillation or have already shown congestive heart failure, there are no clear subdivisions that appear to affect the prognosis in pregnancy. Only 10 per cent of those diagnosed as mitral stenosis had early mitral stenosis according to Lewis' standards—namely, a mitral diastolic murmur heard only after exercise with the patient recumbent. Some of these have had severe congestive heart failure. It is interesting to note that in the group with enlargement of the heart and no valve lesion diagnosed (52 cases), the death rate is 1.9 per cent. Nevertheless, these patients we still believe have deserved Group I cardiac care. The 1.9 per cent death rate has been in spite of such care. Congestive heart failure can appear and has appeared in this group.

Leaving now the question of prognosis—*how do the cardiacs die?* Sixty per cent of the deaths, before the last four years, were in and from congestive heart failure alone. Twenty per cent more died in congestive heart failure with some other important factor—for example, embolism, sepsis, ruptured appendix. Recognizable heart failure in Group I cardiacs in pregnancy has appeared as follows: Five only had the symptom of angina. All five of these had rheumatic heart disease with aortic regurgitation. Five had paroxysmal dyspnea. These had either aortic regurgitation or severe hypertension. No case with uncomplicated mitral stenosis has had proxysmal dyspnea. There have been no sudden unexpected deaths attributable to the heart. Embolism from intracardiac thrombi was diagnosed only twice (both recovered), except in cases with bacterial endocarditis. As Sir James noticed, heart failure in pregnancy appears as congestive heart failure. Though the incidence of heart failure has not greatly diminished with improved care

and markedly lowered maternal mortality, it has changed its degree. Congestive heart failure no longer means the patient described by MacDonald, but an almost subclinical condition discovered by the examining physician. The maternal mortality of all those who had congestive heart failure during pregnancy formerly was 25 per cent. It is now 8 per cent. Heart failure is not what it used to be. The first reliable sign *is* persistent râles at the lung bases. There are earlier signs of failure—diminished vital capacity, Hoover's sign, and perhaps, rarely, increased venous pressure, but they are not reliable. We have tried in many ways to establish some useful earlier criterion, but all we have been able to add to Sir James' statement is the word "reliable."

What makes hearts fail in pregnancy? It is instinctive for a physician faced with a cardiac patient early in pregnancy, or contemplating pregnancy, to direct his attention to the question, "Can this woman stand delivery and the strain of labor?" And indeed there is justification for

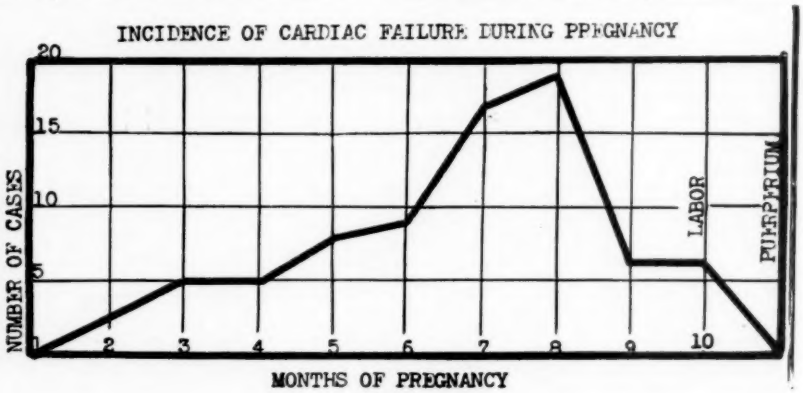

Fig. 1.

this in that 75 per cent of the deaths among the cardiacs occur in the short period of the puerperium. Only 25 per cent die during the months of pregnancy undelivered. The actual load of pregnancy on the circulation shows clearly during the first two-thirds of the last trimester, the blood viscosity and the hematocrit figures fall, and then rise sharply during the last few weeks before term, to continue the rise to normal after delivery with no abrupt change at the time of delivery. Similarly the total blood volume and the cardiac output rise and fall. Most important of all, the time at which recognizable heart failure has clinically appeared in pregnancy agrees with these indirect observations.[3] Failures cluster in the last part of the sixth and in the seventh and eighth months. They rarely begin in the last few weeks. In only four or five cases has failure appeared for the first time during or following the strain of labor and delivery. Delivery and its after effects appear in the study of those cardiacs who die in the puerperium as a good-sized last straw. Delivery will not put them into failure nor kill them unless they are already half dead.

This is a remarkable fact. This actual load of pregnancy should be visualized whenever we face a Group I cardiac early in pregnancy or who is contemplating pregnancy. Furthermore, in individuals the load of pregnancy shows itself, so far as we are able to find it, at varying times and in varying degrees of severity during the dangerous period. This great, varying and inevitable load of course makes it impossible to predict early in pregnancy how any heart will behave, except in a very general sense, by reasoning backward in the light of long experience with clearly defined groups. By no refinement of examination or effort test can we rightfully expect to determine that this or that patient will not develop failure. We can anticipate the coming load and make allowance for it in the regime of the patient. By routine weekly examination—long made a rule—we can watch for and detect failure early and treat it adequately.

Though the failures that occur in Group I cardiacs cluster at the time when the load of pregnancy on the circulation is heaviest, *determining causes for the onset of individual failures* stand out if we take case histories carefully. The same causes occur again and again: (1) Fatigue. One cannot put too much attention on the causes and effective prevention of this vague but vital factor. The commonest factors in fatigue are long shopping trips, moving, opening and closing summer homes, entertaining, sickness in the family. Sudden unusual exertion is a rarer cause. (2) Removable indirect loads on the heart. Overeating with gain in weight, excessive fluid intake, anemia, chronic infection such as oral sepsis, all can be shown to be common and real factors in the production of failure. These factors can be eliminated. The importance of this aspect of the problem cannot be exaggerated. It is unfortunate that it cannot be effectively described in brief.

The Rôle of Intercurrent Infections in Producing Heart Failure and Death.—Every patient has some kind of respiratory tract infection during the nine months of pregnancy or puerperium. If such patients continue to work, a certain number of them show signs of congestive failure. If they go to bed at the onset of the illness, nothing happens. Undoubtedly a severe epidemic such as occurred in 1918 and 1919 would play havoc with the cardiacs in pregnancy, but the epidemics, in the sixteen years that we have followed these cases, have been mild enough so that no death could be directly attributable to them until one death during the last year. Only one has developed pneumococcus pneumonia. This was in the puerperium. She recovered.

I have discussed these rheumatic heart disease cases as though their heart disease were stationary, and indeed it so appears. *In only seven instances have we been tempted to diagnose active rheumatic disease in a pregnant woman.* These were mild affairs. This statement challenges discussion, but it can be abundantly supported. Of course, cases can be found in which an individual, starting with rheumatic disease in

childhood, continues to have recurrences long into adult life and until death. Such cases may have had pregnancies. We find occasionally an individual followed through succeeding pregnancies, with at first nothing but a systolic murmur, years later a mitral diastolic, and later, an aortic diastolic murmur. Such cases are pleasingly scarce. Why do not these women develop active rheumatic disease during pregnancy? They are not the survivors of a group of rheumatic girls followed from the beginning of their disease. They are taken from the whole community—discovered among pregnant women who report to the hospital because they are pregnant and not because they have heart disease or rheumatic disease. Only 50 per cent have an adequate history of having had rheumatic disease. According to our present conviction, they must have had it, but perhaps in a comparatively mild form. In the 50 per cent

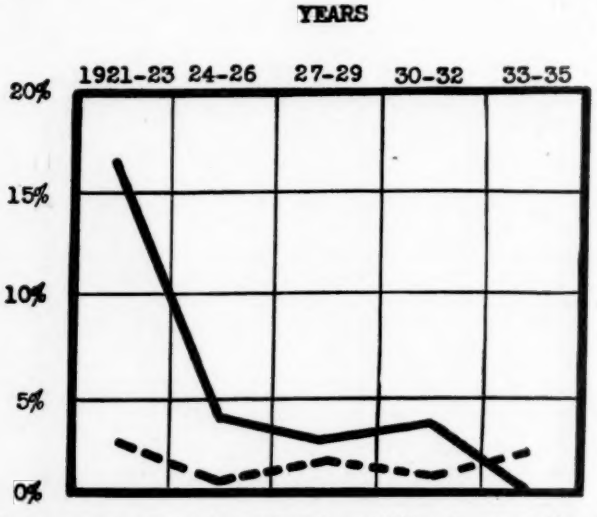

Fig. 2.—Upper curve represents maternal mortality in congestive heart failure per cent cardiacs delivered. Lower curve (interrupted line) represents maternal mortality from causes other than heart failure per cent cardiacs delivered.

that have an adequate history of rheumatic disease, the average age at clinical onset of the disease was thirteen and one-half years. The average age of the Group I cardiacs in pregnancy is between twenty-seven and twenty-eight years. It has been a constant surprise to us to see evidence of activity fail to appear. The inference is that if one thinks of rheumatic disease as seen in medical clinics and, perhaps, at post-mortem study, one may have an exaggerated picture of its persistence and virulence in the adult with chronic rheumatic heart disease.

To return to the prognosis of a Group I cardiac patient in pregnancy. It would appear from all this that after eliminating the clearly bad risks such as described under Group Ia, it should be possible to prevent deaths in congestive failure among Group I cardiacs by regimes designed to anticipate and allow for the load of pregnancy and to prevent the in-

cidental determining factors. And, in fact, deaths from congestive heart failure in pregnancy have been eliminated in this clinic.

There appears to be left a constant minimum death rate of probably close to two and one-half per cent for Group I cardiacs in pregnancy, due to causes other than recognizable heart failure—a death rate ten times higher than the death rate of normal women, as follows:

Just under one per cent of the cardiac patients have shown bacterial endocarditis.

Just under one per cent have had fatal pulmonary embolism. Cardiacs are either more apt to have embolism from venous thrombi or less able to survive them, or both. The incidence is many times higher than among normal women.

Five patients among the first 750 Group I cardiacs delivered died of puerperal sepsis. Only one of these deaths occurred in 600 individuals delivered from below (four-tenths of one per cent); four deaths occurred in 150 delivered by abdominal hysterotomy (two and seven-tenths per cent).

How Shall We Deliver Our Cardiacs?—Though early experience showed that emptying the uterus by abdominal hysterotomy did not cure the failing heart of a mother, it did show that even the worst cases survived the immediate strain of operation. For years we were afraid to let the worst cases go into labor. Improved medical care for the bad risks, a very high infant mortality if delivery occurs before the last two or three weeks, the drop in the load of pregnancy during the last few weeks, with the removal of the reasonable but false preconceived notions that the load increases steadily till term—all these have led us away from the temptation to deliver patients who are bad risks by abdominal hysterotomy before term. And in an attempt to lower the death rate from sepsis in the next sixteen years, we are now trying to avoid abdominal hysterotomy at term for cardiac indications alone. Shall we have thereby a greater number of deaths from heart failure provoked by labor? Only time can tell. Labor can produce heart failure in cardiacs, I have seen it do so—but the present feeling is that cardiacs, even sick cardiacs, stand labor surprisingly well.

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ORGANIC AND RELATIVE INSUFFICIENCY OF THE PULMONARY VALVE*†

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IN THE past, many experienced clinicians and pathologists have considered pulmonary insufficiency as exceedingly rare and its clinical recognition unusually difficult.

Our experience in the wards and at the autopsy table of the Cincinnati General Hospital during the past few years has afforded convincing evidence that pulmonary insufficiency is relatively common and that the diagnosis in cases uncomplicated by other valvular lesions can usually be made during life if one bears the syndrome associated with this disorder in mind. Consequently we shall describe the clinical characteristics of certain of the cases we have had opportunity of observing during life and of proving at autopsy.

Probably the first reference in medical literature to a lesion of the pulmonary valve was made by Morgagni who presented in his treatise "De Sedibus et Causis Morborum," a case of Valsalva's of a young girl "who from birth had experienced great debility, and difficulty of respiration, and the surface of whose body was of a livid tint. The heart was small, and the relative state of the ventricles was reversed; for the right had the usual form of the left, and the left that which usually belongs to the opposite cavity. The capacity of the right auricle was twice that of the left; and its parietes were doubly fleshy. . . . The semilunar valves, at the origin of the pulmonary artery, were slightly ossified, and so united together that only a small foramen, sufficient to admit a lentil was left between them; and at this foramen, small and fleshy membranous productions existed, and were so placed as to act as valves, yielding to the blood as it proceeded from the heart, and resisting its return."[1]

The pathologists of this period apparently realized the infrequency of lesions of the pulmonary valve, as Corvisart is said to have stated that Morgagni was the only author who had observed this condition.

In 1832, James Hope[2] after an able description of aortic, mitral, and tricuspid valvular lesions remarked, "I have never seen the latter [pulmonic valves] diseased, but I have once found them incapable of closing the orifice in consequence of dilatation of the artery."

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†Read before The American Heart Association, Section for the Study of Cardiac Diseases, at Atlantic City, June 8, 1937.

Present day pathologists are in agreement that pulmonary valve lesions are uncommon, especially those of an acquired nature. In an exhaustive survey of the German literature, in 1931, Vellguth[3] concluded that valvular insufficiency of the pulmonary orifice was extraordinarily rare, and cited Finkelstein and Schultze, who found four cases each of pulmonary valve deficiency in 335 and 909 cases, respectively, of heart disease. Herrmann[4] found five cases in 4,776 autopsies at the Charity Hospital in New Orleans, all five of which were apparently rheumatic in origin. Of 24,000 consecutive admissions to the Johns Hopkins Hospital, Hirschfelder[5] found only three cases showing signs of pulmonary regurgitation.

Various classifications of pulmonary insufficiency have been suggested by different authors, but no uniform etiological grouping is as yet established. White states that the lesion may be associated with mitral stenosis; chronic failure of the left ventricle with pulmonary vascular congestion and hypertension; chronic lung disease giving rise to the same mechanical condition; chronic obliterative pulmonary endarteritis; congenital defects of the pulmonary valve giving rise to hypertension; perhaps wide patency of the ductus arteriosus and acute or chronic endocarditis of the pulmonary valve itself. Vaquez classifies the cases into organic and relative insufficiency.

Since the material at our disposal seems better adapted to this terminology, we have accordingly divided our cases into two groups:*

I. Organic Insufficiency: 1. Rheumatic
2. Bacterial
3. Syphilitic

II. Relative Insufficiency: 1. Dilatation of the pulmonary artery secondary to pulmonary arteriosclerosis
2. Mitral stenosis

ORGANIC PULMONARY INSUFFICIENCY

1. *Rheumatic Endocarditis of the Pulmonary Valve*

The occurrence of the rheumatic type of lesion is quite uncommon according to most authorities. Libman[8] in 1923 stated that in his series of cases up to that time the pulmonary valve "was not found affected in any definitely proved cases of rheumatic fever." Poynton and Schlesinger[9] in 1931 stated that ". . . it is exceptional to find vegetations on the pulmonary valve," though they added that "up to the present so little attention has been directed to lesions of the pulmonary valve in active rheumatism that their presence may have been overlooked." Thayer[10] encountered lesions of the pulmonary valve in one of 24 cases of rheumatic endocarditis.

*No congenital lesions of the pulmonary valve were seen, probably owing in great measure to the fact that children are not admitted to the medical wards.

However, in 30 cases of rheumatic heart disease selected at random from the files of the Department of Pathology of the Cincinnati General Hospital lesions of the pulmonary valve were found in 14. In addition to microscopic lesions considered to be definitely rheumatic in these cases and similar to those described by Kugel and Epstein[11] there was gross deformity of the valve in three cases sufficient to produce a regurgitation at the orifice.

CASE 1.—*Summary: Rheumatic endocarditis affecting all valves.* R. W., a sixteen-year-old colored male, was admitted complaining of heart trouble. There was a history of St. Vitus' dance at the age of eight years. Dyspnea and palpitation developed following exertion and exposure to rain. Although the characteristic physical signs of a double mitral lesion were present, one examiner made the diagnosis of relative pulmonary insufficiency because of "a long diastolic murmur accompanied by a diastolic thrill present over the pulmonary area and transmitted down the sternum with a loud pulmonary second sound." A second examiner agreed because of the diastolic murmur in the third left interspace without peripheral signs of aortic insufficiency. Blood pressure was 105/70. Electrocardiogram showed right axis deviation and auricular fibrillation. X-ray films showed the heart to be enlarged in all directions, especially in the region of the left ventricle. Hemoglobin was 90 per cent.

Autopsy revealed gross stenosis in some degree of all four heart valves. Because of the thickening and contraction of the pulmonary valves and absence of peripheral signs of aortic insufficiency it seems logical to believe that the diastolic murmur may have been of pulmonary origin, although the aortic lesion cannot be entirely disregarded. Microscopically no active rheumatic lesions were found anywhere in the heart but there was subsiding activity throughout the substance of the scarred pulmonary valve.

CASE 2.—*Summary: Rheumatic endocarditis affecting all valves.* N. D., a thirty-two-year-old white woman, was admitted because of severe congestive heart failure. The patient stated that she had suffered with heart trouble since an attack of rheumatic fever at the age of eleven. She first complained of palpitation, then shortness of breath and cough. The patient was orthopneic and cyanotic; the pulse irregular, rate 110; blood pressure 128/70. The heart measured 4.5 by 15 cm. to percussion. A diastolic murmur was heard along the left sternal border. P_2 was accentuated. A rough diastolic murmur was also heard below and outside the left sternal border. At the tricuspid area a soft systolic murmur was noted. The liver was enlarged and pulsated. No improvement followed treatment and the patient died forty-eight hours after admission. Electrocardiogram showed right axis deviation with negative T_2 and T_3.

At autopsy acute verrucous endocarditis of the pulmonary valve was found. The verrucae were grossly visible. Microscopically, this case revealed typical rheumatic pancarditis with fresh rheumatic lesions of all of the heart valves.

CASE 3.—*Summary: Rheumatic endocarditis affecting all valves.* J. H., a twenty-five-year-old white laborer, had had dyspnea and ankle edema for four years before his death. The physical findings were characteristic of mitral stenosis and aortic insufficiency.

At autopsy rheumatic pancarditis was demonstrated, all valves being definitely affected. There was marked thickening and retraction of the cusps with stenosis of the pulmonary valve. Microscopically, the pulmonary valve revealed marked thickening, focal fibroblastic proliferation and scarring, with cellular infiltration and vascularization.

2. *Acute Bacterial Endocarditis of Pulmonary Valve*

Acute bacterial endocarditis of the pulmonary valve is stated to be of more common occurrence. In an analysis by Pitt[12] of 109 cases of pulmonary valve disease, 60 were due to infectious endocarditis. In the studies of Thayer[10] on bacterial endocarditis, the pulmonary valve was involved in the following proportions: Gonococcus, 6 of 21 cases; streptococcus, 2 of 34 cases; staphylococcus, 4 of 20 cases; pneumococcus, 1 of 40 cases.

CASE 4.—*Summary: Acute bacterial endocarditis of pulmonary valve (gonorrheal).* J. B., a colored male, aged twenty-eight years, entered the hospital because of acute intestinal obstruction which resulted from adhesions following repair of a gunshot wound of the abdomen. The patient had acquired an active gonorrheal urethritis a month before admission. Following a successful operation he ran a low grade fever for twenty-one days, then signs of pleurisy and consolidation of the left lung base developed. The following day soft systolic and loud diastolic murmurs were heard over the pulmonary area. The diastolic murmur was also audible but fainter in the second right interspace and along the sternal border. A_2 was equal to P_2. Blood pressure was 120/70. X-ray film of the heart was negative. Electrocardiogram showed sinus tachycardia with low voltage of T-waves in Leads II and III; negative T_1. Two blood cultures were negative. The patient ran a down-hill course with symptoms and signs of sepsis and pulmonary infarction. Death occurred after ten weeks in the hospital. The clinical diagnosis was gonorrheal endocarditis of the pulmonary valve and possibly of the aortic valve.

At autopsy, bacterial endocarditis of all four valves was found. The pulmonary valve was so extensively involved that the pathologist recorded "pulmonary valvular insufficiency." Gram-negative and positive rods and streptococci were found in the post-mortem blood culture.

CASE 5.—*Summary: Acute bacterial endocarditis of pulmonary valve.* K. A., a fifty-five-year-old white female, developed weakness, diarrhea, loss of weight, and vomiting during two months preceding admission. Examination revealed pallor, marked purpura, and temperature 102° F. Systolic murmur over the sternum with split pulmonary second sound. Red blood cells numbered 2,000,000, hemoglobin 8 gm. Urine showed occasional red blood cell, albumin 4 plus. Blood culture was negative, blood urea 88. The patient died forty-eight hours after admission.

Autopsy showed the pulmonary valve leaflets to be completely destroyed by vegetations. The organism was not identified.

3. *Syphilis of the Pulmonary Artery*

The incidence of syphilis of the pulmonary artery is extremely uncommon. In 1933, Karsner[13] accepted 11 cases anatomically proved by reasonably liberal interpretation. Brenner[14] in 1935, stated that records of 65 cases of syphilis of the pulmonary artery were found in the literature but that in only 14 of these could the diagnosis be taken as being reasonably well established.

Syphilis may affect the pulmonary artery as a productive cicatricial lesion like the form common in the aorta, or it may be manifested by the formation of gummata. The proliferation type of lesion of the pulmonary artery shows essentially the same changes as those observed in syphilitic aortitis, and usually only the main trunk is involved.

CASE 6.—*Summary: Syphilitic arteritis, pulmonary artery and aorta.* P. F., a normally developed and poorly nourished married negress of about forty-five years of age, was admitted to the Cincinnati General Hospital Nov. 1, 1931, because of congestive heart failure. For about three years prior to admission she had noticed occasional attacks of palpitation, effort dyspnea, infrequent attacks of nocturnal dyspnea, and slight swelling of the feet and ankles. Her general health had been good prior to three months before entering the hospital. There was no history suggesting congenital heart disease, rheumatic fever, or syphilis. Examination revealed orthopnea, cyanosis, and dependent edema extending to about the level of the umbilicus. The cervical veins were engorged and pulsating. The pulpils were equal and reacted to light. A tracheal tug was present and visible pulsations were noted in the episternal notch. The bony framework of the chest was prominent and the apex beat was visible in the sixth left intercostal space about 14 cm. from the midsternal line. In the second and third interspaces on the left there was a visible and forceful pulsation extending 4 to 6 cm. to the left of the midsternal line. No abnormal pulsations were present to the right of the sternum. Over the pulmonic area, in the region of the visible pulsation, a harsh systolic murmur and a blowing diastolic murmur were of maximal intensity. Over the aortic area and at the apex systolic and diastolic murmurs were audible but of less intensity than the murmurs over the second left interspace. The cardiac rate was 40 at the apex and at the wrists. The rhythm was irregular. On the right the blood pressure was 142/80, on the left 182/90. No capillary pulsation was seen and the pulse was not of the Corrigan type. Duroziez's sign was absent. The heart measured 16.5 cm. in the fifth interspace. Congestive râles were present over both bases, and the firm, tender liver edge was easily palpable 3 fingerbreadths below the costal margin. The remainder of the examination was not remarkable except for dependent edema. Blood Wassermann reaction was strongly positive. Red blood cells were 4,500,000, hemoglobin was 80 per cent, white blood cells numbered 6,800. Electrocardiogram showed right axis deviation; complete A-V dissociation; T-waves of low voltage in all leads. X-ray films showed the heart to be markedly enlarged in all directions. The aorta was enlarged but showed no aneurysmal dilatation. On the left a large shadow was superimposed over the aorta in the region of the pulmonary artery which Dr. Hugo Roesler* of Philadelphia identified as an aneurysm of the pulmonary artery (Fig. 1). The last admission was necessitated by extreme dyspnea and precordial pain and the heart sounds became weak, the respirations slow and the patient died quietly.

Anatomical diagnosis: Syphilitic pulmonary arteritis with dilatation of the pulmonary artery (pulmonary valve 100 mm. at orifice, aortic valve 85 mm. at orifice); syphilitic aortitis (clinically aortic and pulmonary insufficiency); syphilitic cirrhosis of the liver; thickening of the pulmonary and aortic valves; cardiac hypertrophy (900 gm.).

RELATIVE PULMONARY INSUFFICIENCY

Relative insufficiency of the pulmonary valves is most frequently secondary to increased intrapulmonary pressure secondary to mitral stenosis. Such insufficiency may be permanent or temporary. In either event the resulting diastolic murmur is called the Graham Steele murmur.

Pulmonary arteriosclerosis may likewise be associated with increase in intrapulmonary pressure, and relative pulmonary insufficiency.

*As far as we can ascertain Dr. Roesler's diagnosis of aneurysm of the pulmonary artery is the first correct diagnosis of this condition before autopsy.

The incidence of pulmonary arteriosclerosis is considered to be approximately that of systemic arteriosclerosis though usually the process is not so severe. This is the type which is part of the picture of generalized vascular atherosclerosis and which does not cause any obvious harmful results. If, however, the extent or situation of the sclerosis causes obstruction to the circulation through the lungs, dilatation and hypertrophy of the right heart will occur, with subsequent signs and symptoms of myocardial failure. This type is known as primary pulmonary arteriosclerosis, or arteriolosclerosis, and is considered to be a rare condition. MacCallum[16] found one case in 12,000 autopsies. According to Brenner[14] there are 16 cases in the literature which can be accepted as fulfilling the criteria for diagnosis.

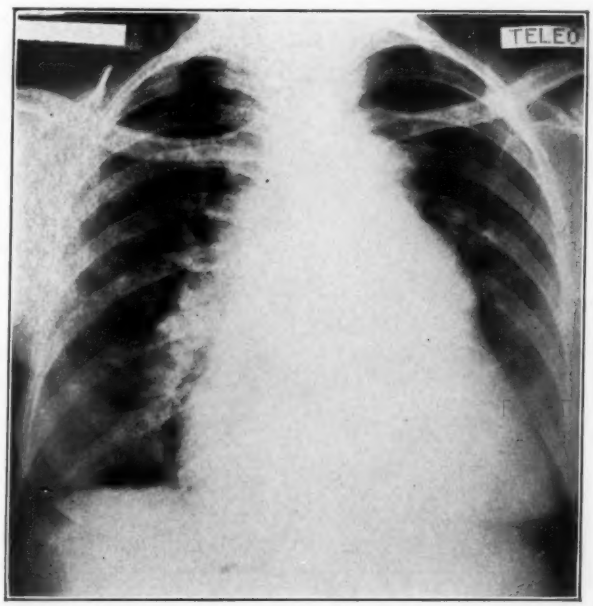

Fig. 1.—Case 6. Teleroentgenogram showing prominent pulmonary conus and branches of pulmonary artery, dilated aorta, and cardiac enlargement.

Karsner[15] divides pulmonary arteriosclerosis into primary, in which the arterioles are involved and in which marked hypertrophy of the right heart is present without demonstrable mechanical or functional cause on gross examination, and secondary, in which the sclerosis is subsequent to chronic diseases of the heart, lung, and pleura. The lesions of secondary pulmonary sclerosis appear principally in the main stems and larger branches of the pulmonary artery.

1. *Pulmonary Arteriosclerosis*

CASE 7.—*Summary: Systemic and pulmonary arteriosclerosis and arteriolosclerosis.* L. H., a forty-four-year-old white housewife, was admitted to the Cincinnati General Hospital in March, 1935 with the complaint of extreme shortness of breath. Effort

dyspnea occurred for the first time in 1931. There was the history of growing pains in childhood, and polyarticular arthritis eight years before, following the birth of her tenth child.

The significant findings were; temperature 99.2, pulse 95, respirations 25, blood pressure 160/120, orthopnea, moderate cyanosis of tongue, lips, fingers, and skin. The lungs showed many medium moist râles at the bases. The heart width measured 18.5 cm., the thoracic width being 31. The pulse was slightly irregular at times (extrasystoles). One examiner reported the classical signs of moderately advanced mitral stenosis at the apex because of a rumbling diastolic murmur at the apex. This murmur was inconstant. P_2 was louder than A_2 and was split at the aortic area. None of the peripheral signs of aortic insufficiency such as Duroziez's sign, capillary pulsation, or pistol-shot sounds were present. X-ray films showed "great enlargement of the left auricle and pulmonary conus. Pulmonary artery is particularly visible. Chronic infiltrative changes in both hilar regions" (Fig. 2). Fluoroscopy

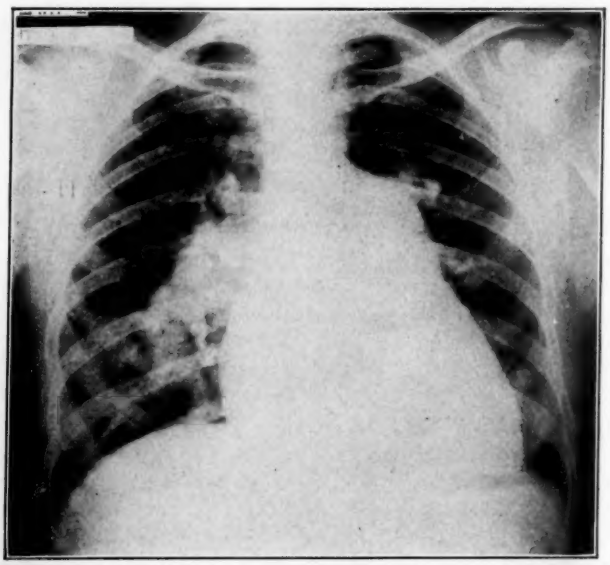

Fig. 2.—Case 7. Teleroentgenogram showing marked prominence of pulmonary conus and cardiac enlargement.

showed the violent pulsations of the branches of the pulmonary artery in the hilum characteristic of pulmonary valvular insufficiency. Electrocardiogram showed right axis deviation; diphasic T_2 and T_3. Red blood cells numbered 5,800,000, hemoglobin was 90 per cent. The patient improved rapidly with digitalis and rest and was sent home. Subsequently she was readmitted on three occasions because of dyspnea and edema. On the last admission she died suddenly and unexpectedly. The clinical diagnosis was "pulmonary valvular insufficiency, probably organic."

Autopsy: Heart weight 575 gm. Pulmonary orifice dilated, measuring 95 mm., the aortic valve measuring 70 mm. Myocardium of the right ventricle greatly hypertrophied. Marked atherosclerosis of the pulmonary artery. Thrombi present in both branches of the pulmonary artery. The failure of the right ventricle in this case may be attributed to a combination of factors, chronic failure of the left ventricle with pulmonary congestion and an increased right ventricular strain, very possibly associated with pulmonary hypertension.

CASE 8.—*Summary: Primary pulmonary arteriolosclerosis.* P. O'H., a forty-two-year-old white male, was admitted with a productive cough of ten years' duration. There had been dyspnea on exertion for six years. The patient had been deaf and dumb since birth. Examination showed cyanosis, moderate cardiac enlargement, systolic murmurs, and thrill maximum in third left interspace. P_2 was accentuated. Electrocardiogram showed right axis deviation. X-ray films showed prominence of the pulmonary conus with cardiac enlargement (Fig. 3). Red blood cells numbered 4,500,000, hemoglobin was 80 per cent (Sahli). Clinical diagnosis: Congenital pulmonic stenosis; lobar pneumonia.

Autopsy: Unresolved lobar pneumonia with empyema; pulmonary arteriolosclerosis with right ventricular hypertrophy and dilatation. The pulmonary valve orifice measured 115 mm., the aortic 60 mm.

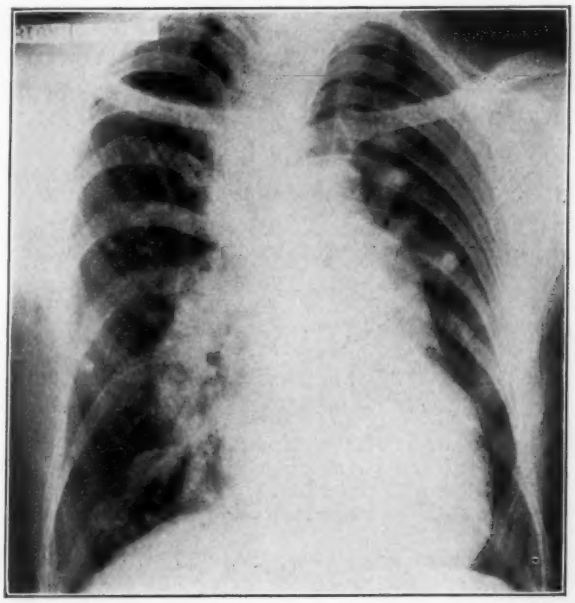

Fig. 3.—Case 8. Teleroentgenogram showing prominent pulmonary conus and dilatation of branches of pulmonary artery in right hilum. There is moderate scoliosis.

2. *Mitral Stenosis With Graham Steele Murmur*

CASE 9.—*Summary: Mitral stenosis with dilatation of pulmonary artery.* R. D., a forty-six-year-old white male, gave the history of dyspnea, cough and weakness followed by edema of ankles over a period of five years. There was moderate cardiac enlargement and the characteristic signs of mitral stenosis. A long, blowing diastolic murmur was heard along the left sternal border, maximal in the third to fourth interspace. Blood pressure was 100/80. There was absence of peripheral signs of aortic valvulitis. Electrocardiogram showed right axis deviation. X-ray films showed straight left cardiac silhouette and enlargement of the right heart. Clinical Diagnosis: Mitral stenosis with relative pulmonary insufficiency (Graham Steele murmur).

Autopsy: Cardiac hypertrophy, especially of the right heart; mitral and aortic stenosis; dilatation of pulmonary artery and pulmonic orifice (90 mm.).

SUMMARY

The pathological and clinical features of 9 cases of pulmonary insufficiency have been presented. The lesion is ordinarily considered very unusual, yet 4 cases have been observed in the Cincinnati General Hospital within the past year.

The etiological factors found in this series of cases were: Rheumatic fever, bacterial endocarditis, pulmonary arteriolosclerosis; systemic and probably pulmonary hypertension; syphilitic pulmonary arteritis, and mitral stenosis.

In all the cases caused by rheumatic fever there were clinical signs of involvement of more than one valve. Lesions of all four valves were found at autopsy in each case. The presence of multiple valvular lesions makes the diagnosis of pulmonary insufficiency very difficult.

There were no symptoms in our cases characteristic of pulmonary insufficiency per se. The symptoms depended upon the existing disease process and the degree of myocardial insufficiency.

The clinical features characterizing pulmonary insufficiency were a diastolic murmur in the second left interspace transmitted towards the axilla, accentuation of the pulmonary second sound, prominence of the pulmonary conus, marked pulsation of the hilum vessels, and right axis deviation of the electrocardiogram.

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AN UNUSUAL CASE OF AURICULAR PARASYSTOLE SHOWING "EXIT" BLOCK*

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CONSIDERABLE controversy has existed regarding the mechanism responsible for frequent ectopic premature beats (Wenckebach and Winterberg,[1] Lewis,[2] and Rothberger[3]). While the idea of occasional haphazard awakening of dormant ectopic pacemakers has been advocated and the view of re-entry has been promulgated to explain fixed coupling, the Viennese school led by Rothberger has put forth the concept that many forms of premature systoles and paroxysmal tachycardias are due to the constant activity of a secondary pacemaker (or pacemakers) competing with the sinus pacemaker for control of the heart. This is the fundamental concept of parasystole. In its simplest form as developed by Kaufmann and Rothberger,[4] parasystole presupposes the formation of rhythmic stimuli at an abnormal focus at a frequency measured by the shortest time interval between two ectopic beats. The longer intervals (during which sinus beats intervene between the ectopic beats) are multiples of the shorter time intervals and arise because of interference by the sinus impulse. Activation of the heart by the ectopic impulse when it falls in the refractory period of the heart follows stimulation by the sinus. The continuous activity of the secondary pacemaker, contrary to ordinary conditions, and the failure of the sinus impulse to obliterate or affect it, demand the existence of an "entrance" or "protection" block *(Eintritts* or *Schützblockierung)* around the ectopic pacemaker. In some instances an inherent rate of the ectopic pacemaker faster than the sinus rate has been assumed to explain the timing of ectopic beats, and this has demanded the view that some of the impulses from the ectopic pacemaker are blocked, not because the entire chamber (auricle or ventricle) is in the refractory phase (interference), but because of a localized block, a so-called "exit" block *(Austrittsblockiering),* preventing the impulse from leaving the pacemaker.

While the ideas of interference and protection block have ample evidence to support them (cf. case reports[4, 5, 6, 7, 8, 9]), no direct clear evidence of exit block exists, as the cases cited by Kaufmann and Rothberger[4] to support this view have been criticized by Singer and Winterberg.[5]

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Aided by the A. D. Nast Fund for Cardiac Research.

Recently we have seen a patient who has had over a period of years sinus bradycardia, intraventricular block, multiple active ectopic pacemakers of the auricle and ventricle, and attacks of auricular flutter and paroxysmal tachycardia. On one occasion the electrocardiogram clearly demonstrated exit block. We are therefore presenting the case report with the pertinent electrocardiograms and tabular summaries of our measurements in order to lend support to the existence of parasystole with exit block.

CASE REPORT

The patient was first seen by one of us (H. B.) in association with Dr. Sol Strouse in the fall of 1926. He was fifty-seven years of age at that time. His complaints at that time were of indefinite pains in the abdomen which were considered to be genitourinary in origin. He had had tuberculosis in his early youth. He showed evidence of arteriosclerosis with cardiac enlargement, a slow pulse, and a blood pressure of 175/100. In the spring of 1927 he had pus cells in his urine and later developed uremia. He was operated upon; an infected patent urachus was removed and a prostatectomy was performed. His recovery was uneventful. His blood pressure fell to 140/80. In the fall of 1928 on x-ray examination a duodenal ulcer was noted. In the spring of 1930 he had an anemia due to a hemorrhage from this.

In the summer of 1932, he returned complaining for the first time of pain in the chest (1 cm. to the left of the heart's apex); this spot was also tender. No change was noted in the heart findings; the x-ray examination showed a dilated aorta. An electrocardiogram taken at this time showed intraventricular block of the common bundle-branch type with frequent ventricular and auricular extrasystoles from multiple foci. (This will be discussed in detail below.) The patient stated that irregularity of his heart had been noted as far back as 1899. In 1933 he had trouble with hemorrhoids and complained also of precordial and abdominal distress. His heart had been slow and irregular whenever he was examined. During this period treatment was directed toward the relief of the duodenal ulcer.

In 1934 his cardiac symptoms came to the fore, and his ulcer symptoms receded. During the winter, he had a flare-up of his pulmonary tuberculosis with fever, râles in the right infrascapular region, and tubercle bacilli in the sputum. He went to a spa over the winter and returned in the spring of 1935 much improved. His cardiac examination was unchanged. During a visit to New York in May, his cough returned. In August he had a sudden attack of shortness of breath and felt very ill. He was seen at his home by one of us (S. H. R.), who found the pulse rapid and râles in the upper chest bilaterally. The pulse quickly returned to its normal rate. The patient was kept in bed for several days.

In the fall of 1935 another attack occurred, and the patient was seen by two of us (S. S. and H. B.). He had cyanosis, dyspnea, and râles in the infrascapular regions and at both bases; his pulse was irregular and at times bigeminal. He recovered from this attack on rest in bed. He had several electrocardiograms taken afterward which were similar in general character to the one taken in 1932, except in one there was a paroxysm of ventricular extrasystoles.

In the spring of 1936 he had another "heart" attack with tachycardia and dyspnea, from which he gradually recovered with bed rest, morphine, and digitalis. The four-lead electrocardiogram taken at this time had the chief clue to the mechanism of his irregularity. From this time on he was under the care of one of us (S. S.). A new attack of tachycardia and heart failure was induced in August, 1936, by excitement. On bed rest, morphine, and large doses of digitalis his condition improved. In September he had an attack of tachycardia, the pulse going to 122-144

(his normal rate being 44-60. At the slow rate of 44, the heart usually showed a bigeminus). It stayed at this rapid rate for several days. Quinidine 3 gr. every two hours was given. At the same time a source of great apprehension was removed, and the pulse became slow within a few hours. During the tachycardia, carotid sinus pressure and breath holding both caused transitory slowing. The mechanism appeared to be auricular flutter. After that the patient had several attacks of paroxysmal tachycardia; these were controlled by quinidine. An electrocardiogram taken during one showed the mechanism to be auricular flutter with 2:1 conduction. A long four-lead electrocardiogram containing 425 ventricular beats was taken at this period.

On physical examination during the winter of 1936, the left border of the heart was found to be 15 cm. from the midsternal line, the right, 4 cm. His cardiothoracic ratio in the x-ray film was 16/31. He had many calcified tuberculous nodules throughout both lungs. A blowing systolic murmur was heard at the apex. His blood pressure was 130-180/80. The liver was palpable 2 or 3 fingerbreadths below the costal margin.

The diagnosis at this time made by one of us (S. S.) was: (1) arteriosclerotic heart disease (coronary sclerosis); (2) cardiac hypertrophy; (3) extrasystoles and auricular flutter (neurogenic?); (4) healed pulmonary tuberculosis; and (5) healed duodenal ulcer.

The patient went to California for the winter. There he acquired an embolus in his left brachial artery, his left hand and fingers became numb, and he had pain in this arm above the elbow. No radial or cubital pulse was felt on this side. A short while later his cardiac symptoms and signs recurred in severe form; coma developed; and death occurred within several days. No autopsy was obtained.

ANALYSIS AND INTERPRETATION OF ELECTROCARDIOGRAMS

The electrocardiograms taken on May 20, 1936, and on July 7, 1932, are shown in Figs. 1 and 2, respectively, and Figs. 3 to 8 show portions of the long four-lead electrocardiogram taken on Oct. 26, 1936.

1. Electrocardiogram Taken May 20, 1936.—The most significant electrocardiogram is the one shown in Fig. 1, since inspection of this record led one of us (L. N. K.) to suspect the presence of parasystole with exit block, and measurements confirmed this impression. It will be seen that in each lead there are two types of P-waves, those marked *P* and those marked (*P*). (The nature of P_{11} in Lead I is in doubt; it may be a fusion form.) The QRS complexes are all alike and show the typical characteristics of intraventricular block of the common bundle-branch type.

Accurate measurements were made of all the P-P intervals, and the results are shown in Fig. 1 and are assembled in Table I. It is apparent that there are four kinds of P-P intervals: viz. (1) P-P, (2) (P)-P, (3) (P)-(P) and (4) P-(P); these were separated from each other in summarizing the measurements.

It was soon apparent that the P-P intervals, of which there were eight (Table II), were all equal in duration (1.28 sec.) except one which was 0.04 sec. less. It was also obvious that the (P)-P intervals were equal in duration or a trifle longer than the P-P intervals; viz. 1.24 to 1.36 sec. (Table III). It was, therefore, concluded that the auricular waves marked *P* were sinus in origin, that the auricular waves marked (*P*) were

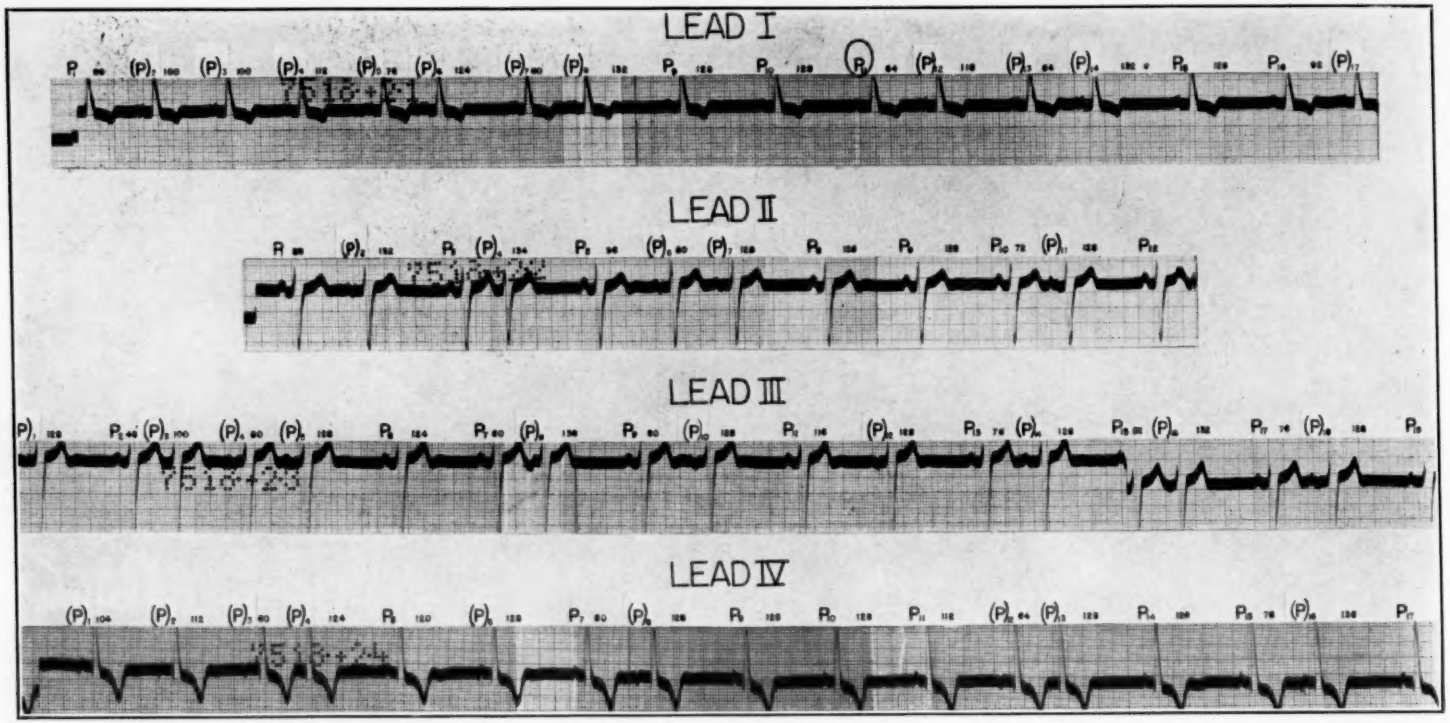

Fig. 1.—Electrocardiogram (four-lead) taken on this patient on May 20, 1936. Above each lead is marked each P-wave, and the figures between give the interauricular interval ×100. The two types of origin of the impulses are designated as *P* for the sinus and *(P)* for the parasystolic origin. P_{11} in Lead I is probably a fusion form. (?) indicates inability to time P-wave accurately. Discussed in text.

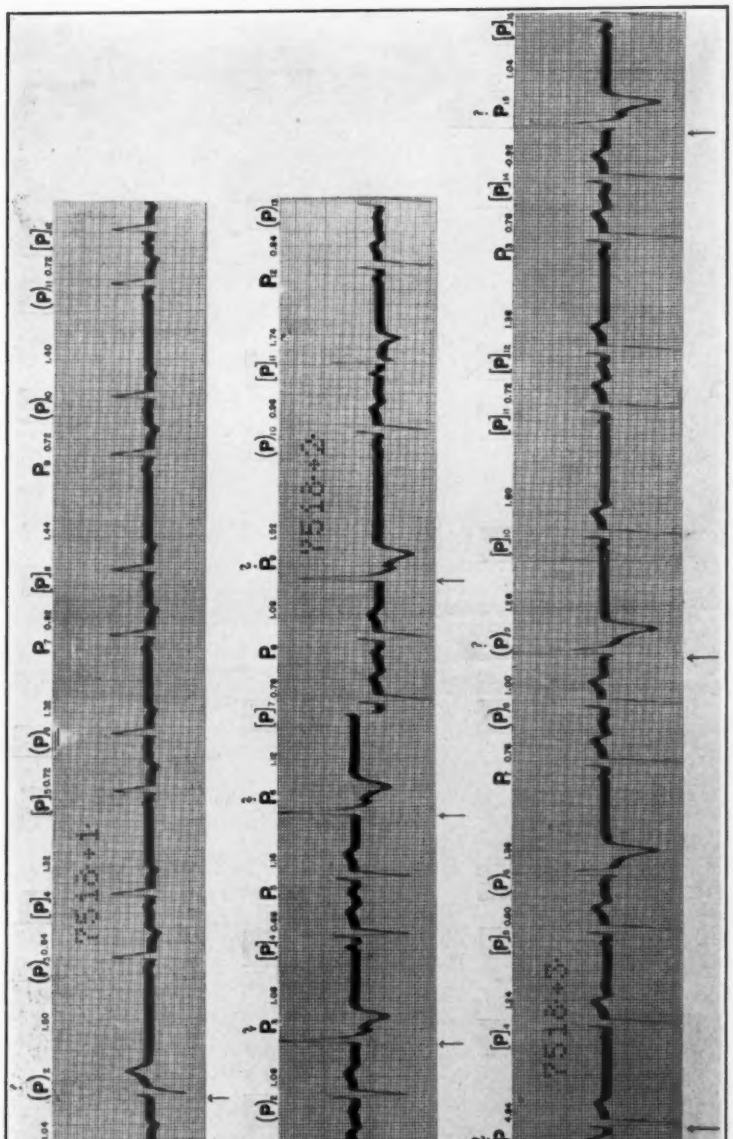

Fig. 2.—Electrocardiogram (three-lead) taken on this patient on July 7, 1932, showing three parasystolic rhythms indicated by *P*, *(P)* and *[P]*. The interauricular intervals are marked as in Fig. 1. The P-waves with ? above cannot be identified as to origin. Below each lead the ventricular ectopic beats are indicated by upright arrows. Discussed in text.

TABLE I

INTERVAL BETWEEN ALL P-WAVES (FIG. 1)

LEAD I		LEAD II		LEAD III		LEAD IV	
INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.
P_1-P_2	0.88	P_1-P_2	0.88	P_1-P_2	1.28	P_1-P_2	1.04
P_2-P_3	1.00	P_2-P_3	1.32	P_2-P_3	0.48	P_2-P_3	1.12
P_3-P_4	1.00	P_3-P_4	0.46	P_3-P_4	1.00	P_3-P_4	0.60
P_4-P_5	1.12	P_4-P_5	1.34	P_4-P_5	0.80	P_4-P_5	1.24
P_5-P_6	0.76	P_5-P_6	0.96	P_5-P_6	1.28	P_5-P_6	1.20
P_6-P_7	1.24	P_6-P_7	0.80	P_6-P_7	1.24	P_6-P_7	1.28
P_7-P_8	0.80	P_7-P_8	1.28	P_7-P_8	0.60	P_7-P_8	0.80
P_8-P_9	1.32	P_8-P_9	1.28	P_8-P_9	1.36	P_8-P_9	1.28
P_9-P_{10}	1.28	P_9-P_{10}	1.28	P_9-P_{10}	0.80	P_9-P_{10}	1.28
P_{10}-P_{11}	1.28	P_{10}-P_{11}	0.72	P_{10}-P_{11}	1.28	P_{10}-P_{11}	1.28
P_{11}-P_{12}	0.84	P_{11}-P_{12}	1.28	P_{11}-P_{12}	1.16	P_{11}-P_{12}	1.12
P_{12}-P_{13}	1.16			P_{12}-P_{13}	1.28	P_{12}-P_{13}	0.64
P_{13}-P_{14}	0.84			P_{13}-P_{14}	0.76	P_{13}-P_{14}	1.28
P_{14}-P_{15}	1.32			P_{14}-P_{15}	1.28	P_{14}-P_{15}	1.28
P_{15}-P_{16}	1.28			P_{15}-P_{16}	0.52	P_{15}-P_{16}	0.76
P_{16}-P_{17}	0.92			P_{16}-P_{17}	1.32	P_{16}-P_{17}	1.36
				P_{17}-P_{18}	0.76		
				P_{18}-P_{19}	1.28		

TABLE II

P-P INTERVALS (FIG. 1)

LEAD I		LEAD II		LEAD III		LEAD IV	
INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.
P_9-P_{10}	1.28	P_8-P_9	1.28	P_6-P_7	1.24	P_9-P_{10}	1.28
P_{15}-P_{16}	1.28	P_9-P_{10}	1.28			P_{10}-P_{11}	1.28
						P_{14}-P_{15}	1.28

1.24 = 48 per minute.
1.28 = 47 per minute.

TABLE III

(P)-P INTERVALS (FIG. 1)

LEAD I		LEAD II		LEAD III		LEAD IV	
INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.	INTERVAL	DURATION IN SEC.
P_8-P_9	1.32	P_2-P_3	1.32	P_1-P_2	1.28	P_4-P_5	1.24
P_{14}-P_{15}	1.32	P_4-P_5	1.34	P_5-P_6	1.28	P_6-P_7	1.28
		P_7-P_8	1.28	P_8-P_9	1.36	P_8-P_9	1.28
		P_{11}-P_{12}	1.28	P_{10}-P_{11}	1.28	P_{13}-P_{14}	1.28
				P_{12}-P_{13}	1.28	P_{16}-P_{17}	1.36
				P_{14}-P_{15}	1.28		
				P_{16}-P_{17}	1.28		
				P_{18}-P_{19}	1.28		

1.24 = 48 per min.
1.28 = 47 per min.
1.32 = 46 per min.
1.34 = 45 per min.
1.36 = 44 per min.

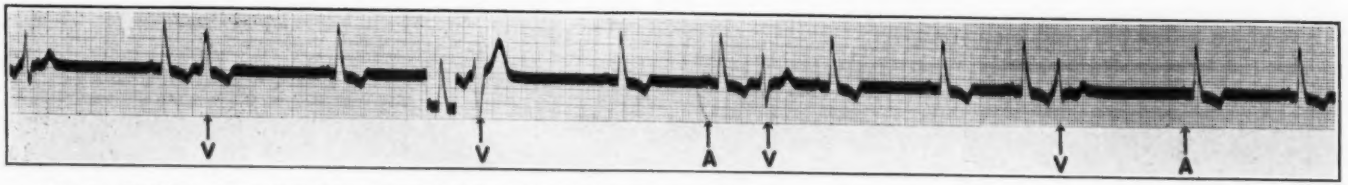

Fig. 3.—Portion of Lead I taken on Oct. 26, 1936, to show two auricular and four ventricular ectopic pacemakers identified respectively by upright arrows marked *A* and *V*. Discussed in text.

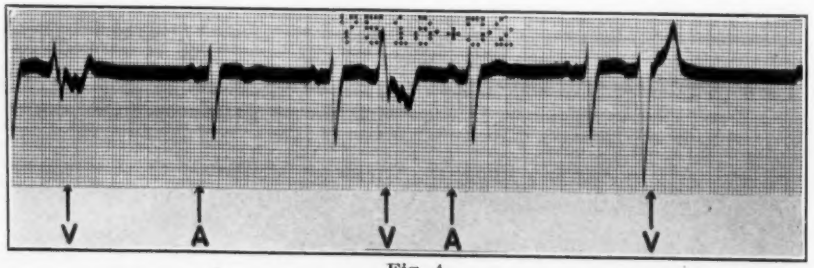

Fig. 4.

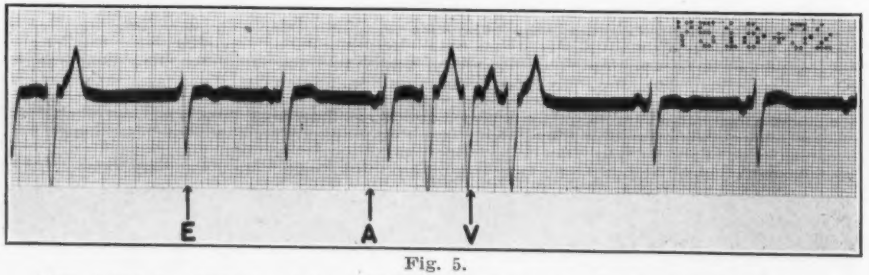

Fig. 5.

Figs. 4 and 5.—Portions of Lead II taken on Oct. 26, 1936, to show three auricular and four ventricular ectopic pacemakers identified as in Fig. 3. *E* indicates a nodal escape. Discussed in text.

from a focus close to the sinus node, and that the (P)-P intervals were similar to the interval following an auricular premature systole arising close to the sinus node. No correlation could be made in regard to the P-(P) intervals.

The (P)-(P) intervals (Table IV), it will be seen, are multiples of a cycle length equal to 0.16 sec. ± 0.01, which is equivalent to a parasystolic rhythm with a rate of 375 per minute (which incidentally was the auricular flutter rate found during an attack). There is, therefore, an exit block giving rise to a ratio of total impulses over those conducted of from 4:1 to 8:1.

TABLE IV

(P)-(P) INTERVALS (FIG. 1)

LEAD I				LEAD II			
INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS OF PARASYSTOLIC RHYTHM	CYCLE LENGTH OF PARASYSTOLIC RHYTHM	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS OF PARASYSTOLIC RHYTHM	CYCLE LENGTH OF PARASYSTOLIC RHYTHM
P_2-P_3	1.00	6:1	0.17	P_6-P_7	0.80	5:1	0.16
P_3-P_4	1.00	6:1	0.17				
P_4-P_5	1.12	7:1	0.16				
P_5-P_6	0.76	5:1	0.15				
P_6-P_7	1.24	8:1	0.16				
P_7-P_8	0.80	5:1	0.16				
P_{11}-P_{12}	0.84	5:1	0.17				
P_{12}-P_{13}	1.16	7:1	0.17				
P_{23}-P_{24}	0.84	5:1	0.17				
LEAD III				**LEAD IV**			
P_3-P_4	1.00	6:1	0.17	P_1-P_2	1.04	6:1	0.17
P_4-P_5	0.80	5:1	0.16	P_2-P_3	1.12	7:1	0.16
				P_3-P_4	0.60	4:1	0.15
				P_{12}-P_{13}	0.64	4:1	0.16

0.15 = 400 beats per minute.
0.16 = 375 beats per minute.
0.17 = 353 beats per minute.

In brief, to recapitulate, the auricular waves marked (P) in Fig. 1 are thus sinus in origin, and those marked P are ectopic. The fact that the calculated cycle length for the parasystolic rhythm varies ± 0.01 sec. is not surprising on biological grounds and because the error in measuring the interauricular intervals amounts to 0.02 sec. In line with the idea that this is a parasystolic rhythm is the fact that the longest (P)-(P) interval was shorter than the usual P-P interval, indicating that the sinus node was kept discharged by the parasystolic rhythm and only took hold when the exit block increased to a degree permitting the sinus node to escape.

When the (P)-(P) intervals, during which some sinus P-waves occur, were measured [(P)-P-(P)] (Table V), it was found that they too could be

resolved into multiples of a cycle length of 0.16 sec. ± 0.01 sec., indicating again a constantly active pacemaker going at the rate of 375 per minute. This indicates the presence of entrance or protection block around the parasystolic pacemaker, preventing the sinus impulse from discharging the ectopic one, and the usual form of interference which prevents the ectopic pacemaker from acting on the heart for anywhere from 11 to 31 of its cycles.

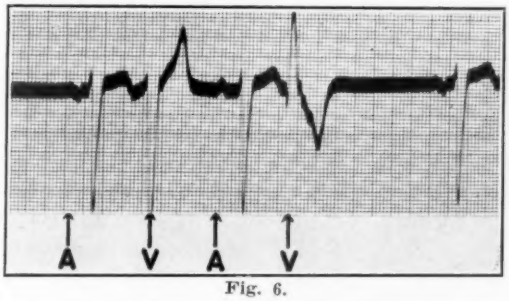

Fig. 6.

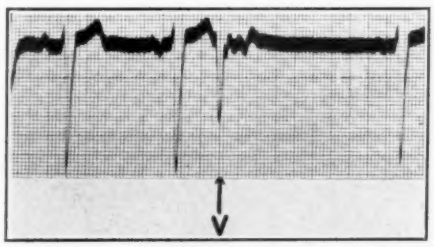

Fig. 7.

Figs. 6 and 7.—Portions of Lead III taken on Oct. 26, 1936, to show two auricular and three ventricular ectopic pacemakers identified as in Fig. 3. Discussed in text.

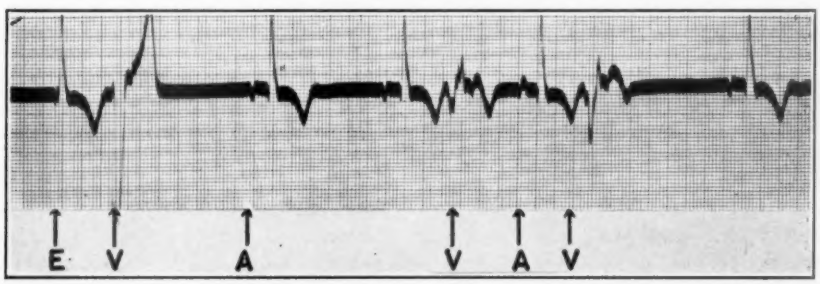

Fig. 8.—Portion of Lead IV taken on Oct. 26, 1936, to show two out of three auricular and three ventricular ectopic pacemakers identified as in Fig. 3. *E* indicates a nodal escape. Discussed in text.

The shortest interval between two P-waves in this record occurred in Lead II between P_3 and $(P)_4$. This interval of 0.46 sec. represents the shortest duration of the refractory phase following a sinus beat and is equal to slightly less than three parasystolic cycles. The exit block was longer than this while this record was taken; the least degree was such as to block three out of four impulses of the parasystolic rhythm, but

sometimes it was such as to drop seven out of eight impulses. The paroxysmal auricular flutter in this case occurred when the exit block disappeared (or at least had a refractory phase shorter than 0.16 sec., the cycle length of the parasystolic rhythm). It is obvious that in such

TABLE V

(P)-P-(P) INTERVALS (FIG. 1)

LEAD I			LEAD II		
INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM
P_8-P_{11}	3.88	22 × 0.16	P_2-P_4	1.78	11 × 0.16
P_{14}-P_{17}	3.52	24 × 0.16	P_4-P_6	2.30	14 × 0.16
			P_7-P_{11}	4.56	28 × 0.16
LEAD III			LEAD IV		
P_1-P_3	1.76	11 × 0.16	P_4-P_6	2.44	15 × 0.16
P_5-P_8	3.12	19 × 0.16	P_6-P_8	2.08	13 × 0.16
P_8-P_{10}	2.16	14 × 0.15	P_8-P_{12}	4.96	31 × 0.16
P_{10}-P_{12}	2.44	15 × 0.16	P_{13}-P_{16}	3.32	21 × 0.16
P_{12}-P_{14}	2.04	13 × 0.16			
P_{14}-P_{16}	1.80	11 × 0.16			
P_{16}-P_{18}	2.08	13 × 0.16			

0.16 = 375 beats per minute.

cases circus movement need not be invoked to explain the flutter, since a single focus mechanism as formulated by the Viennese school could adequately account for the flutter mechanism.

Figure 9 is a diagrammatic representation of our interpretation of the arrhythmia occurring in this patient when Fig. 1 was taken. *E* above shows the parasystolic rhythm with the exit block indicated by the middle horizontal line; the beats that come through are shown by the downward directed arrows. The sinus beats are shown by the upward directed arrows, and the lower horizontal line indicates the entrance block protecting the parasystolic rhythm. The interference for possession of the heart between the sinus and parasystolic rhythms can readily be worked out from this diagram.

2. Electrocardiogram Taken Oct. 26, 1936.—The conditions existing when this record was taken were more complex than five months earlier. Several auricular and ventricular pacemakers were found to exist at this time among the 424 beats measured and analyzed. In Lead I we were able to identify two auricular (*A*) and four ventricular (*V*) pacemakers (Fig. 3); in Lead II, three auricular and four ventricular pacemakers as well as a nodal escape (*E*) (Figs. 4 and 5); in Lead III, two auricular and three ventricular pacemakers (Figs. 6 and 7); in Lead IV, three auricular and three ventricular pacemakers, as well as a nodal escape (Fig. 8 shows only two of the three auricular pacemakers). The records also show the presence of intraventricular block of the common bundle-branch type.

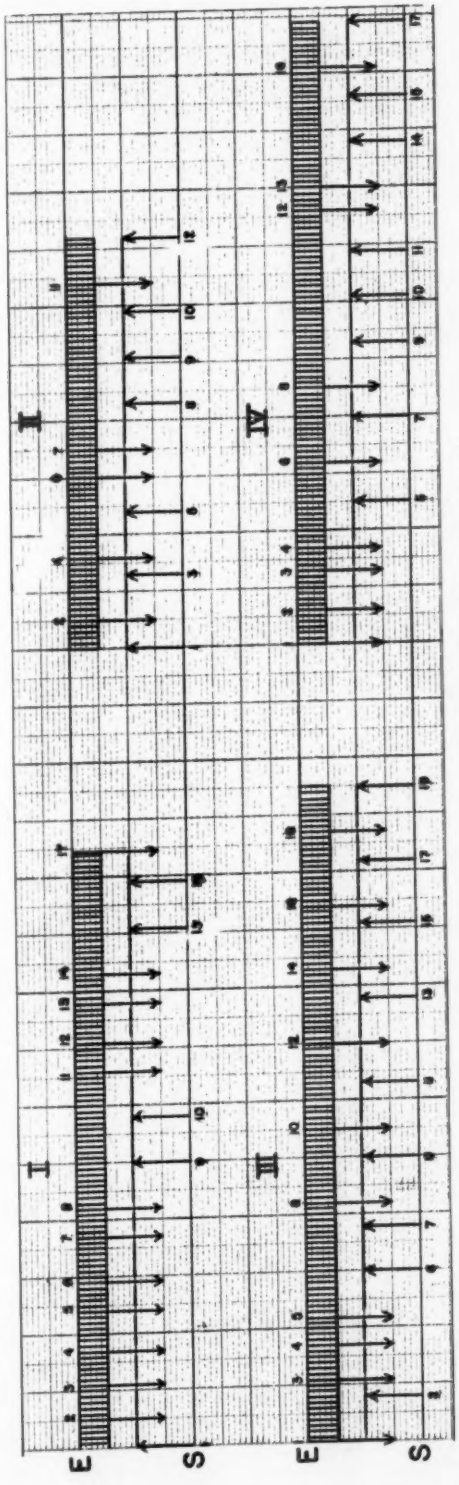

Fig. 9.—Diagram of mechanism of Fig. 1. Discussed in text.

TABLE VI

P-P INTERVALS OF FIRST FOCUS OF PARASYSTOLE (FIGS. 3-8)

LEAD	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM
I.	P_1-P_3	2.08	10 × 0.21
	P_3-P_5	2.36	12 × 0.20
	P_5-P_6	1.08	5 × 0.22
	P_6-P_9	3.64	18 × 0.20
	P_9-P_{12}	3.80	19 × 0.20
	P_{12}-P_{14}	2.44	12 × 0.20
	P_{14}-P_{15}	1.40	7 × 0.20
	P_{15}-P_{19}	3.80	19 × 0.20
	P_{19}-P_{20}	1.00	5 × 0.20
	P_{20}-P_{23}	3.56	17 × 0.21
	P_{23}-P_{24}	1.24	6 × 0.21
	P_{24}-P_{25}	1.16	6 × 0.20
	P_{25}-P_{28}	3.88	19 × 0.20
	P_{28}-P_{32}	3.76	19 × 0.20
	P_{32}-P_{33}	1.40	7 × 0.20
	P_{33}-P_{37}	3.84	19 × 0.20
	P_{37}-P_{38}	1.48	7 × 0.21
	P_{38}-P_{40}	2.24	11 × 0.20
	P_{40}-P_{44}	3.96	20 × 0.20
	P_{44}-P_{45}	1.44	7 × 0.21
	P_{45}-P_{49}	3.84	19 × 0.20
	P_{49}-P_{50}	1.24	6 × 0.21
	P_{50}-P_{51}	1.28	6 × 0.21
	P_{51}-P_{52}	1.04	5 × 0.21
	P_{52}-P_{53}	0.56	3 × 0.20
	P_{53}-P_{66}	2.96	15 × 0.20
	P_{56}-P_{57}	1.12	5 × 0.22
	P_{57}-P_{61}	4.84	24 × 0.20
	P_{61}-P_{65}	5.16	26 × 0.20
	P_{65}-P_{69}	4.16	21 × 0.20
	P_{69}-P_{72}	3.92	19 × 0.21
	P_{74}-P_{78}	3.56	17 × 0.21
	P_{78}-P_{79}	1.08	5 × 0.22
	P_{79}-P_{83}	5.04	25 × 0.20
	P_{83}-P_{84}	1.04	5 × 0.21
	P_{84}-P_{88}	5.36	26 × 0.21
	P_{88}-P_{91}	3.72	18 × 0.21
	P_{91}-P_{92}	1.12	5 × 0.22
	P_{92}-P_{95}	3.92	19 × 0.21
	P_{95}-P_{96}	1.20	6 × 0.20
	P_{96}-P_{105}	8.72	42 × 0.21
	P_{105}-P_{107}	2.40	12 × 0.20
	P_{107}-P_{108}	1.20	6 × 0.20
II.	P_3-P_4	1.36	6 × 0.23
	P_4-P_7	2.80	14 × 0.20
	P_7-P_{10}	4.04	20 × 0.20
	P_{10}-P_{11}	1.32	6 × 0.22
	P_{11}-P_{12}	1.04	5 × 0.21
	P_{12}-P_{18}	6.40	32 × 0.20
	P_{18}-P_{19}	1.40	7 × 0.20
	P_{19}-P_{21}	2.60	13 × 0.20
	P_{21}-P_{22}	1.52	8 × 0.19
	P_{22}-P_{26}	4.56	23 × 0.20
	P_{26}-P_{27}	1.44	7 × 0.21
	P_{27}-P_{33}	6.28	31 × 0.20
	P_{33}-P_{34}	1.48	7 × 0.21
	P_{34}-P_{35}	1.36	6 × 0.23
	P_{35}-P_{42}	7.40	37 × 0.20
	P_{42}-P_{43}	1.05	5 × 0.21
	P_{43}-P_{45}	2.04	10 × 0.20
	P_{45}-P_{46}	1.40	7 × 0.20
	P_{46}-P_{50}	5.08	25 × 0.20
	P_{50}-P_{51}	1.12	5 × 0.22
	P_{51}-P_{56}	9.56	48 × 0.20
	P_{56}-P_{58}	3.52	17 × 0.21
	P_{58}-P_{65}	10.56	50 × 0.21
	P_{65}-P_{67}	3.32	16 × 0.21
	P_{67}-P_{77}	10.92	54 × 0.20
	P_{77}-P_{81}	3.76	18 × 0.21
	P_{81}-P_{82}	1.36	6 × 0.23
	P_{82}-P_{84}	2.48	12 × 0.21
	P_{84}-P_{85}	1.24	6 × 0.21
	P_{85}-P_{86}	1.24	6 × 0.21
	P_{86}-P_{90}	4.68	23 × 0.20
	P_{90}-P_{91}	1.44	7 × 0.21
	P_{91}-P_{93}	2.20	11 × 0.20
	P_{93}-P_{94}	1.28	6 × 0.21
III.	P_1-P_3	2.56	12 × 0.21
	P_3-P_4	1.40	7 × 0.20
	P_4-P_7	3.16	16 × 0.20
	P_7-P_9	2.92	14 × 0.21
	P_9-P_{15}	6.24	31 × 0.20
	P_{15}-P_{16}	1.32	6 × 0.22
	P_{16}-P_{18}	2.44	12 × 0.20
	P_{18}-P_{19}	1.44	7 × 0.21
	P_{19}-P_{26}	8.28	41 × 0.20
	P_{26}-P_{27}	1.32	6 × 0.22
	P_{27}-P_{28}	1.08	5 × 0.22
	P_{28}-P_{34}	6.40	32 × 0.20
	P_{34}-P_{35}	1.24	6 × 0.21
	P_{35}-P_{36}	1.08	5 × 0.22
	P_{36}-P_{39}	3.92	19 × 0.21
	P_{39}-P_{43}	3.84	19 × 0.20
	P_{43}-P_{44}	1.48	7 × 0.21
	P_{44}-P_{46}	2.32	11 × 0.21
	P_{46}-P_{48}	2.36	11 × 0.21
	P_{48}-P_{49}	1.36	6 × 0.23
	P_{49}-P_{53}	3.76	18 × 0.21
	P_{53}-P_{54}	1.44	7 × 0.21
	P_{54}-P_{56}	2.40	12 × 0.20
	P_{56}-P_{57}	1.44	7 × 0.21
	P_{57}-P_{60}	3.88	19 × 0.20
	P_{60}-P_{64}	4.20	21 × 0.20
	P_{64}-P_{68}	1.48	7 × 0.21
	P_{65}-P_{68}	2.72	13 × 0.21
	P_{68}-P_{74}	6.20	31 × 0.20
	P_{74}-P_{75}	1.48	7 × 0.21
	P_{75}-P_{79}	3.76	18 × 0.21
	P_{84}-P_{85}	0.88	4 × 0.22
	P_{85}-P_{87}	2.28	11 × 0.21
	P_{87}-P_{91}	3.92	19 × 0.20
	P_{91}-P_{92}	1.24	6 × 0.21
	P_{92}-P_{99}	7.84	39 × 0.20
	P_{99}-P_{103}	3.76	18 × 0.21

TABLE VI—CONT'D

	LEAD INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM	LEAD INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM
	P_{102}-P_{103}	1.28	6 × 0.21	P_{27}-P_{28}	1.36	7 × 0.20
	P_{103}-P_{105}	2.24	11 × 0.20	P_{28}-P_{29}	1.08	5 × 0.22
	P_{105}-P_{107}	2.32	11 × 0.21	P_{29}-P_{31}	2.24	11 × 0.20
	P_{107}-P_{108}	1.40	7 × 0.20	P_{31}-P_{32}	1.36	7 × 0.20
	P_{108}-P_{115}	7.20	36 × 0.20	P_{32}-P_{34}	2.36	11 × 0.21
	P_{115}-P_{116}	1.20	6 × 0.20	P_{34}-P_{35}	1.40	7 × 0.20
	P_{116}-P_{120}	5.12	25 × 0.20	P_{35}-P_{40}	5.16	25 × 0.21
	P_{120}-P_{121}	1.24	6 × 0.21	P_{40}-P_{41}	1.16	6 × 0.20
	P_{121}-P_{123}	1.24	6 × 0.21	P_{41}-P_{44}	3.36	16 × 0.21
	P_{122}-P_{124}	2.32	11 × 0.21	P_{44}-P_{46}	2.36	11 × 0.21
	P_{124}-P_{126}	2.20	11 × 0.20	P_{46}-P_{50}	3.76	18 × 0.21
	P_{126}-P_{127}	1.36	6 × 0.23	P_{50}-P_{51}	1.40	7 × 0.20
	P_{127}-P_{131}	3.88	19 × 0.20	P_{51}-P_{52}	1.08	5 × 0.22
	P_{131}-P_{132}	1.20	6 × 0.20	P_{52}-P_{54}	2.20	11 × 0.20
				P_{54}-P_{55}	1.16	6 × 0.20
IV.	P_1-P_3	2.40	12 × 0.20	P_{55}-P_{61}	5.74	28 × 0.21
	P_3-P_4	1.08	5 × 0.22	P_{61}-P_{62}	1.32	6 × 0.22
	P_4-P_6	2.32	11 × 0.21	P_{62}-P_{63}	1.44	7 × 0.21
	P_6-P_7	0.80	4 × 0.20	P_{63}-P_{64}	1.16	6 × 0.20
	P_7-P_8	1.28	6 × 0.21	P_{64}-P_{66}	2.44	12 × 0.20
	P_8-P_9	1.40	7 × 0.20	P_{66}-P_{67}	1.04	5 × 0.21
	P_9-P_{13}	3.60	18 × 0.20	P_{67}-P_{72}	6.29	31 × 0.20
	P_{13}-P_{14}	1.40	7 × 0.20	P_{72}-P_{73}	1.24	6 × 0.21
	P_{14}-P_{16}	2.48	12 × 0.21	P_{73}-P_{77}	4.92	24 × 0.21
	P_{16}-P_{19}	3.68	18 × 0.21	P_{77}-P_{78}	1.40	7 × 0.20
	P_{19}-P_{20}	1.04	5 × 0.21	P_{78}-P_{84}	6.88	34 × 0.21
	P_{20}-P_{24}	4.68	23 × 0.20	P_{84}-P_{88}	3.92	19 × 0.21
	P_{24}-P_{25}	1.36	7 × 0.20	P_{88}-P_{89}	0.88	4 × 0.22
	P_{25}-P_{27}	2.40	12 × 0.20			

0.19 = 316 beats per minute.
0.20 = 300 beats per minute.
0.21 = 286 beats per minute.
0.22 = 272 beats per minute.
0.23 = 261 beats per minute.

All the P-P intervals of the various auricular and all the R-R intervals of the various ventricular pacemakers were measured. While it was easy to find common divisors for both the auricular and ventricular pacemakers in each lead, it was not possible to match the ventricular pacemakers of one lead with those of the others with any degree of certainty. We, therefore, can only surmise that a number of parasystolic foci were operating in the ventricles, interfering with one another (and with the impulses coming to the ventricle via the A-V junctional tissue) for possession of the ventricles. There was no conclusive evidence of exit block in these ventricular foci, the cycle length of the parasystolic rhythms being sufficiently long so that interference of the various foci could explain all the findings.

In the case of the auricular parasystolic rhythms, the 242 cycle measured in the various leads could be divided into three types, each with its own common divisor (Tables VI, VII and VIII). No evidence of a sinus rhythm could be made out; apparently the auricles were entirely under the control of these three parasystolic rhythms competing with

each other. While interference alone might have explained the occurrence of the heartbeats arising from one of these foci, exit block has to be invoked in the other two, if our calculations of the cycle length of the parasystolic rhythms are correct.

3. Electrocardiogram Taken July 7, 1932.—It is interesting that the record taken four and one-half years before (Fig. 2) also showed three auricular pacemakers which on analysis show common divisors approximately equal to those found on Oct. 26, 1936 (Table IX). This would indicate that these parasystolic rhythms had been present for at least four and one-half years. Ventricular extrasystoles were also present at this time but were not as frequent or from as many foci as in the long record referred to above.

TABLE VII

P-P INTERVALS OF SECOND FOCUS OF PARASYSTOLE (FIGS. 3-8)

LEAD	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM
II.	P_{54}-P_{60}	10.72	26 × 0.41
	P_{60}-P_{68}	11.60	29 × 0.40
	P_{68}-P_{72}	4.64	11 × 0.42
	P_{72}-P_{74}	1.24	3 × 0.41
III.	P_{6}-P_{8}	2.16	5 × 0.43
	P_{8}-P_{11}	3.84	9 × 0.43
	P_{11}-P_{13}	1.48	4 × 0.37
	P_{13}-P_{21}	9.16	22 × 0.42
	P_{21}-P_{23}	2.52	6 × 0.42
	P_{23}-P_{25}	2.64	7 × 0.38
	P_{25}-P_{30}	6.28	15 × 0.42
	P_{30}-P_{32}	1.56	4 × 0.39
	P_{32}-P_{38}	7.12	18 × 0.40
	P_{38}-P_{41}	3.12	8 × 0.39
	P_{41}-P_{51}	11.32	29 × 0.39
	P_{51}-P_{59}	10.00	25 × 0.40
	P_{59}-P_{62}	2.96	7 × 0.42
	P_{62}-P_{67}	5.64	14 × 0.40
	P_{67}-P_{70}	3.60	9 × 0.40
	P_{70}-P_{72}	1.52	4 × 0.38
	P_{72}-P_{77}	5.10	13 × 0.39
	P_{77}-P_{81}	4.80	12 × 0.40
	P_{82}-P_{89}	7.16	18 × 0.40
	P_{89}-P_{95}	6.48	16 × 0.41
	P_{95}-P_{96}	1.44	4 × 0.36
	P_{96}-P_{98}	2.52	6 × 0.42
	P_{98}-P_{101}	3.68	9 × 0.41
	P_{101}-P_{110}	9.96	25 × 0.40
	P_{110}-P_{113}	2.88	7 × 0.41
	P_{113}-P_{114}	1.64	4 × 0.41
	P_{114}-P_{118}	4.92	12 × 0.41
	P_{118}-P_{129}	12.44	31 × 0.40
IV.	P_{11}-P_{18}	8.56	21 × 0.41
	P_{18}-P_{22}	4.56	11 × 0.42
	P_{22}-P_{37}	17.40	43 × 0.40
	P_{37}-P_{39}	1.48	4 × 0.37
	P_{39}-P_{43}	4.76	12 × 0.40
	P_{43}-P_{48}	4.84	12 × 0.40
	P_{48}-P_{59}	12.04	30 × 0.40
	P_{59}-P_{69}	12.01	30 × 0.40
	P_{69}-P_{71}	2.56	6 × 0.43
	P_{71}-P_{75}	4.96	12 × 0.41
	P_{75}-P_{80}	5.36	13 × 0.41
	P_{80}-P_{82}	2.36	6 × 0.39
	P_{82}-P_{83}	1.56	4 × 0.39
	P_{83}-P_{86}	3.00	7 × 0.43

0.37 = 162 beats per minute.
0.38 = 158 beats per minute.
0.39 = 154 beats per minute.
0.40 = 150 beats per minute.
0.41 = 146 beats per minute.
0.42 = 143 beats per minute.
0.43 = 140 beats per minute.

SUMMARY

A case is reported of arteriosclerotic heart disease with sinus bradycardia and intraventricular block which on one occasion showed an electrocardiogram with an auricular parasystole competing with the sinus rhythm. Evidence is given that the parasystolic focus was beating at

TABLE VIII

P-P INTERVALS OF THIRD FOCUS OF PARASYSTOLE (FIGS. 3-8)

LEAD	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM
I.	P_{11}-P_{17}	6.60	9 × 0.73
	P_{17}-P_{22}	5.36	7 × 0.77
	P_{22}-P_{27}	6.36	8 × 0.80
	P_{27}-P_{30}	2.92	4 × 0.73
	P_{30}-P_{35}	5.24	7 × 0.75
	P_{35}-P_{47}	12.92	17 × 0.76
	P_{47}-P_{55}	7.80	10 × 0.78
	P_{55}-P_{59}	5.12	7 × 0.73
	P_{59}-P_{67}	9.12	12 × 0.76
	P_{67}-P_{68}	1.56	2 × 0.78
	P_{68}-P_{71}	3.56	5 × 0.71
	P_{71}-P_{76}	3.06	4 × 0.74
	P_{76}-P_{81}	5.52	7 × 0.79
	P_{81}-P_{86}	6.08	8 × 0.76
	P_{86}-P_{87}	1.56	2 × 0.78
	P_{87}-P_{94}	8.76	12 × 0.73
	P_{94}-P_{98}	4.12	5 × 0.82
	P_{98}-P_{100}	2.40	3 × 0.80
	P_{100}-P_{102}	1.56	2 × 0.78
	P_{102}-P_{104}	2.44	3 × 0.81
II.	P_{1}-P_{6}	5.16	7 × 0.74
	P_{6}-P_{9}	3.80	5 × 0.76
	P_{9}-P_{14}	6.36	8 × 0.80
	P_{14}-P_{16}	1.52	2 × 0.76
	P_{16}-P_{24}	10.36	14 × 0.74
	P_{24}-P_{29}	6.04	8 × 0.76
	P_{29}-P_{31}	1.56	2 × 0.78
	P_{31}-P_{38}	8.80	12 × 0.73
	P_{38}-P_{40}	1.48	2 × 0.74
	P_{40}-P_{48}	8.24	11 × 0.75
	P_{48}-P_{62}	23.68	32 × 0.74
	P_{62}-P_{72}	12.60	17 × 0.74
	P_{72}-P_{79}	7.72	10 × 0.77
	P_{79}-P_{88}	11.04	15 × 0.74
IV.	P_{2}-P_{10}	9.24	12 × 0.77
	P_{10}-P_{15}	5.08	7 × 0.73
	P_{15}-P_{26}	13.28	17 × 0.78
	P_{26}-P_{85}	67.97	90 × 0.76
	P_{85}-P_{87}	1.56	2 × 0.78

0.71 = 85 beats per minute.
0.73 = 82 beats per minute.
0.74 = 81 beats per minute.
0.75 = 80 beats per minute.
0.76 = 79 beats per minute.
0.77 = 78 beats per minute.
0.78 = 77 beats per minute.
0.79 = 76 beats per minute.
0.80 = 75 beats per minute.
0.81 = 74 beats per minute.
0.82 = 73 beats per minute.

the rate of 375 per minute and had exit block (as postulated by Kaufmann and Rothberger). This is apparently the first case with definite evidence of exit block on record.

An electrocardiogram taken subsequently showed sinus rhythm absent and gave evidence of multiple auricular and ventricular foci of impulse initiation. Three auricular and at least four ventricular foci were identified as well as an occasional nodal escape. The parasystolic character of the ventricular rhythms was suggested by the evidence but could not be established with certainty since the cycles in each lead were too few and the beats in one lead could not be accurately identified with beats in other leads. The three auricular rhythms could be shown on the basis of measurements of 242 cycles to be parasystolic in origin with exit block present in at least two of them.

A record taken about four and one-half years before showed the same three auricular parasystolic rhythms occurring at approximately the same rate. This demonstrates the long persistence of parasystolic pacemakers.

The attacks of rapid heart action in this patient, which resembled paroxysmal tachycardia and auricular flutter, seem to be correlated with lessening of the exit block at least in the case of the auricular rhythms.

TABLE IX

P-P INTERVALS OF THREE FOCI OF PARASYSTOLES (FIG. 2)

FIRST FOCUS				SECOND FOCUS				THIRD FOCUS			
LEAD	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM	LEAD	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM	LEAD	INTERVAL	DURATION IN SEC.	RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM
I.	P_4-P_5	1.32	6 × 0.22	I.	P_3-P_6	2.88	7 × 0.41	I.	P_7-P_9	2.26	3 × 0.75
	P_5-P_{12}	7.14	31 × 0.23		P_6-P_8	2.14	5 × 0.43		P_9-P_{11}	2.12	3 × 0.71
					P_8-P_{10}	2.16	5 × 0.43				
II.	P_1-P_4	2.88	13 × 0.22					II.	P_5-P_8	3.04	4 × 0.76
	P_4-P_7	2.96	13 × 0.23	II.	P_2-P_{10}	8.44	21 × 0.40		P_8-P_{12}	4.60	6 × 0.77
	P_7-P_{11}	4.12	19 × 0.22		P_{10}-P_{13}	2.84	7 × 0.41				
III.	P_4-P_5	1.24	6 × 0.21	III.	P_2-P_3	0.84	2 × 0.42	III.	P_9-P_{13}	6.72	9 × 0.75
	P_5-P_{10}	5.20	23 × 0.23		P_3-P_6	5.08	14 × 0.42				
	P_{10}-P_{11}	1.60	7 × 0.23		P_6-P_8	2.12	5 × 0.42				
	P_{11}-P_{12}	0.72	3 × 0.24		P_8-P_{14}	6.72	16 × 0.42				
	P_{12}-P_{16}	4.08	19 × 0.21								

0.21 = 286 beats per minute.
0.22 = 272 beats per minute.
0.23 = 261 beats per minute.
0.24 = 250 beats per minute.

0.40 = 150 beats per minute.
0.41 = 146 beats per minute.
0.42 = 143 beats per minute.
0.43 = 140 beats per minute.

0.71 = 85 peats per minute.
0.75 = 80 beats per minute.
0.76 = 77 beats per minute.
0.77 = 76 beats per minute.

This case we believe lends support to the parasystolic theory expounded by Rothberger and his colleagues and seems to give clear proof of the existence of exit block.

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THE ELECTRICAL AXIS IN SIMULTANEOUS LEADS

I. Factors Increasing the Dispersion of Normal Values*

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INTRODUCTION

A CONSPICUOUS feature of the electrocardiogram that both invites computation and resists analysis is the difference in amplitude of its component waves. This problem presents two phases, the origin of the primary distinction between individual portions of a single cycle, and the source of the secondary modifications to which each wave is susceptible. Since the most sensitive index for the description of these waves is found in the electrical axis, for the measurement of which suitable apparatus has not been generally available, further study is in order.

As recognized by Einthoven and his coworkers[1] (1913), the shape of an electrocardiogram is conditioned by the position of the electrodes in relation to the heart. This is in accord with the proposition that the passage of an electrical current in a given circuit will exert a maximum effect upon electrodes in a secondary circuit if that is parallel to the first, and the current will have no effect upon a secondary circuit placed at right-angles to itself (Millikan and Mills, p. 15[2]). Conversely, if the orientation of the primary circuit were unknown it could be discovered by moving the secondary electrodes about it until the maximum effect was obtained: then the axis connecting these electrodes will be parallel to the primary or electrical axis (Trendelenburg, 1932-33[3]). In the case of the heart the direction of the flow of the electrical impulse may be similarly discovered but it is not necessary to rotate the electrodes because, by using Einthoven's triangular arrangement of the electrodes it is possible to calculate the electrical axis from the three standard leads. This principle accounts for the altered appearance of a given wave in different leads.

It is also known (Kahn 1909,[4] Fahr 1912,[5] Williams 1914,[6] Lewis 1925, chapter 8, p. 123, 127;[7] Meek and Wilson 1925[8]) that the electrical axis of the heart is not constant throughout the cycle, varying from instant to instant as though the spread of the excitation wave followed a changing (i. e., nonrectilinear) course. Assuming that the Purkinje system constitutes the excitation pathway it is obvious that certain regions will lie parallel to one of the three standard leads (Robb, Greene and Robb, 1937[9]). Hence, these regions will be fully represented in the corresponding lead. On the other hand, all those pathways not

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in the frontal plane will be less adequately recorded, and those portions of the Purkinje system that lie at right angles to the frontal plane will have little, if any, effect on any standard lead. The former regions probably correspond to the "favored regions" of Katz and his associates[10] and the latter portions would constitute the "silent areas" of coronary thrombosis. These conclusions offer a theoretical justification for the use of chest leads; furthermore, the changing direction of the excitation wave during each cycle offers a physical basis on which to explain the differences of amplitude and duration characteristic of the several component waves of an electrocardiogram.

SOURCES OF ERROR

It is obvious that the progress of excitation in the heart is a three dimensional phenomenon which is also a function of time. If the electrical axis be defined as the apparent direction of the excitation wave, one must concede that its satisfactory description requires four dimensions. Most of the published observations include only the two dimensions of the frontal plane, intercepted at an arbitrary point in time which is assumed to be comparable in clinical tracings. It is not surprising that tremendous normal variations are accepted. Thus, applying Einthoven's equation to the R-waves alone,

Einthoven, Fahr, and De Waart[1] give as normal	40 to 90°
Waller[11]	–10 to 100°
Carter, Richter, and Green,[12] Dieuaide[23]	0 to 90°
Lewis[7]	75 (about)
Pardee[13]	30 to 90°
Proger and Davis[14]	0 to 80°
White[15]	0 to 90°

Even if it be assumed that the axis of the R-wave is peculiarly sensitive to abnormal conditions outside the bundle of His, its evaluation presents major difficulties, each of which contributes to the dispersion of normal values.

1. *Phase Error.*—It is often impossible to identify synchronous points in the several leads unless they were recorded simultaneously. Thus White (1937, p. 130) mentions that the leads are frequently "out of phase." This is evidenced by lack of conformity to the equation: $E^2 = E^1 + E^3$ (Wilson, McLeod, Barker, 1931-32[16]). Williams (1914[6]) reports 5 cases in 6 out of phase. We have noted this discrepancy in about 60 per cent of the electrocardiograms published by Carter (1937[17]) and in 80 per cent of those given by Pardee (1933[18]). In all of these records no legitimate calculation of the "R-axis" is possible, because, as shown in Fig. 1, there is no one R-axis to measure. If, as in a recent patient, the three R-waves, 1, 2, and 3 are 3, 6 and 6 mm. respectively, who can say which one (or two) values are misleading? Regarding

this contingency Jones and Roberts (1929[19]) remark "rarely do perpendiculars of all three leads fall on one point; it is simpler to use only Leads I and II." Herrmann and Wilson[20] suggest the use of the two largest, and Proger and Davis (1930[14]) prefer Leads I and II in cases of left ventricular preponderance and II and III in right ventricular preponderance as previously suggested by Pardee (1920[13]). Unless simultaneous points are recognizable there exists no legitimate method for calculating any axis in out-of-phase records.

2. *Inconsistency in Calculation.*—It is not permissible to include in a single class for comparison electrical axes calculated by different methods, because R may have a different value in each lead, as shown in Table I.

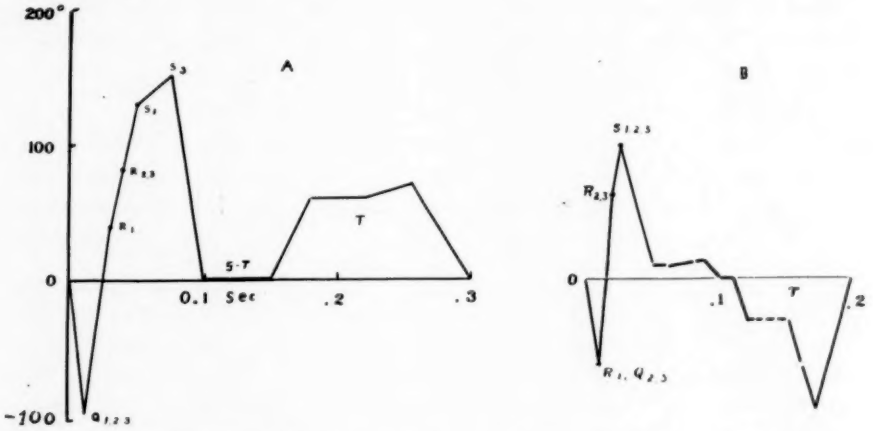

Fig. 1.—Electrical axes plotted at 2 to 10 sigma intervals throughout the (ventricular) cycle; *A:* man, *B:* a dog with negative T.

Note that the R_1 and R_3-peaks of the standard leads were not synchronous, and have axes differing 50 and 100°, respectively.

In five of these six records the axis of R_3 differs from that of R_1 by about one hundred degrees. These details are obscured when some hybrid estimate is attempted, as is the current usage; such estimates have no real existence and very little empirical value. Thus Carter's[17]

TABLE I

DISCREPANCIES BETWEEN METHODS OF CALCULATING ELECTRICAL AXES IN OUT-OF-PHASE RECORDS

	R-PEAKS, AS IN CONSECUTIVE RECORDS		HOMOLOGOUS POINTS, AS IN SIMULTANEOUS RECORDS		
Patient	$R^1 + R^2$	$R^2 + R^3$	R^1	R^2	R^3
A	0*	33	4	12	-90
B	6*	44	-42	48	70
C	20*	40	17	40	120
D	20*	44	16	16	150
E	30*	56	30	48	120
F	84	94*	60	93	104

*Asterisk denotes angle derived by calculation from the two largest peaks; numbers represent degrees from the horizontal, advancing clockwise from the left side.

prime examples of right axis deviation, given in his Fig. 18, in order of severity, calculated from Leads I and II are: 65, 74, 81, 83, and 85°; recalculated from II and III, these are: 86, 85, 85, 95, and 102°. None of these is far beyond the "normal" range. Similarly his illustrations of left axis deviation in Fig. 21 may be calculated as: 55, 40, 23, 20, and 25° in I and II; or: 55, 40, –25, –28, –38° in Leads II and III, showing that an unchallenged alternative method of interpretation may introduce a fifty degree discrepancy. It is suggested that in every out-of-phase record the method of calculation be indicated, and better still, if homologous points are available, the axis offered for consideration should be carefully designated as, e. e.: R_1–R_2, R_1–R_3, R_3–Q_1, etc.

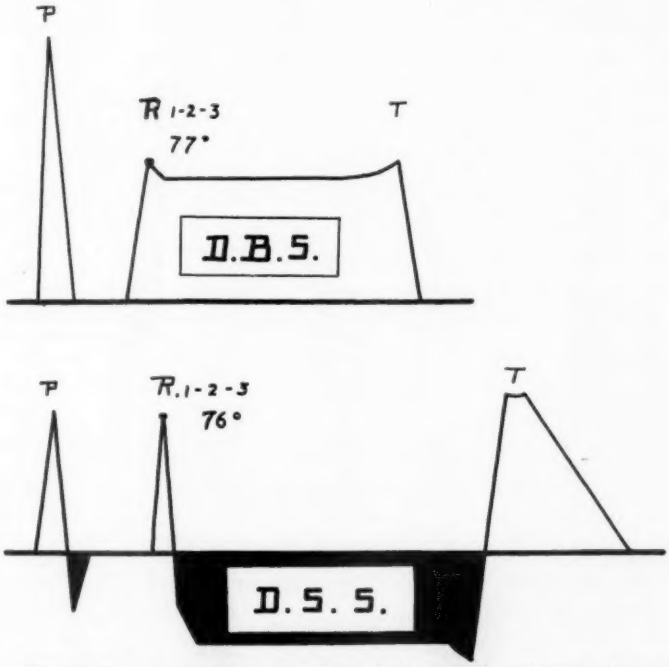

Fig. 2.—Electrical axes plotted at about 0.01 second intervals throughout the cycle, with negative angles below the base line. Upper curve: dog with deep bulbospiral muscle infarct; lower curve: another dog with deep sinospiral muscle injured. Note that in both the R-wave axes are identical but the S-T axes are displaced in opposite directions (although each lesion is on the left side of the heart).

3. *The Indifference of the R-wave to Peripheral Lesions.*—The inference is inescapable that, if the electrical axis has any significance whatsoever, its behavior throughout the entire cycle will be more instructive than at any one point. In Fig. 2 it is evident that the axis (of R) is identical in two dogs following acute infarctions of the deep sinospiral muscle in one heart and of the deep bulbospiral in the other, although other regions of the axis are strongly contrasted. (Incidentally, this observation refutes the suggestion[21] that the S-T displacements of infarction are associated with rotation of the heart itself

because the visible absence of gross rotation is here corroborated by the internal evidence of an unchanged R-axis. This figure does show that the one region of the electrical axis usually inspected may be indifferent to gross pathology known to exist beyond the major branches of the bundle of His.

4. *Apparatus.*—Evaluation of the electrical axis for an entire cycle (at intervals of 0.005 to 0.010 second) is arduous without simultaneous records by two or more balanced galvanometers (having identical string periodicity, and circuits of *equal resistance* to avoid shunting deformity of the records), focussed on a single camera with a common time marker to avoid parallax. In reading the data an accurate measuring instrument is desirable.

It is significant that de Waart,[22] using three simultaneous leads has reported a remarkably narrow range of normal values for the R-axis in the *Macaca irus,* between 50 and 75° with an average of about 70°. We have been able to confirm his figures in monkeys of another species (*Macacus rhesus*), and we have observed a similarly restricted range for the R-axis in normal dogs. It is our hope that an understanding of the human electrocardiogram may be extended by a rigorous adherance to precautions such as are outlined in this paper.

SUMMARY AND CONCLUSIONS

I. The wide variation in the values accepted as normal for the electrical axis is ascribed, in large measure, to improper and inconsistent treatment of the data.

1. In approximately three-fourths (74 ± 5 per cent) of one hundred recently published electrocardiograms the R-peaks of the standard leads are out-of-phase. In such cases there exists no satisfactory method for calculating this axis.

2. When the R-peaks are out-of-phase (so that E_2 is not the sum of $E_1 + E_3$), each R may have an axis of its own that differs some 50 to 100° from the others.

3. In such cases, the arbitrary selection of any two leads from which to calculate an axis produces some unreal number that may differ 50° from that derived from another person's interpretation of the same tracing. This accounts for a considerable part of the reported variation.

II. It is also probable that too much has been expected of the R-wave and its axis.

1. It must be remembered that the axis can not reflect conditions that exist at right angles to the frontal plane when only standard leads are employed, because secondary electrodes record electrical events best when in a parallel direction and least of all when perpendicular. Since much of the Purkinje system deviates from the frontal plane, preferential and "silent" areas are created by the orientation of the very electrodes used to explore them.

2. Furthermore, the peak of the R-wave, together with its electrical axis, may be entirely unresponsive to experimental infarction of the deep bulbospiral or deep sinospiral muscles, although these lesions markedly affect the axis in *a later* portion of the cycle.

3. Apparently there is no close correlation (and no good reason to expect such a relation) between the R-axis and peripheral lesions not involving the main branches of the bundle of His.

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THE SYMBALLOPHONE: A MODIFIED STETHOSCOPE FOR THE LATERALIZATION AND COMPARISON OF SOUNDS*

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IT IS well known that the direction from which a sound comes is determined chiefly by the difference in time required for the sound waves to reach the tympanic membrane of the two ears and register in the brain as sound. The variation in intensity of the sound reaching the two ears is probably of lesser importance in determining the source of external sounds.

We have made use of these principles in the construction of a new type of stethoscope for comparison of two areas over the heart and lungs. Preliminary observations indicate that differences in timing of sounds from the two areas compared can be used to determine the point of origin of sounds and the direction of propagation. This infomation should be of practical importance in clinical medicine. The principles may also be applied in other fields where the point of origin of sounds and the direction of travel of sound are of interest.

In 1910, Muralt[1] devised a stethoscope which permitted the physician to listen simultaneously to two areas over the lungs. This stethoscope consisted of two endpieces or acoustic bells with tubes running from each bell to both ears. It is apparent from his illustrations that the crossed tubes to the opposite ears were equal in length to the tubes passing directly from one endpiece to the ear on the same side. Sounds originating in one endpiece reached both ears simultaneously. More recently, Fröschels[2] suggested the use of a "differential stethoscope" which is essentially a pair of endpieces each connected to the ear by a single tube and each passing through an X or four-way connection which permits either an ipso- or contralateral course of the sound to each ear. This instrument was devised to study the sounds produced in the vocal cords in the detection of laryngeal paralysis.

Nicolai[3] devised a "stereostethoscope" to detect differences in sounds originating in the two mandibular joints, and suggested its use in other fields of clinical medicine. This instrument consisted of two endpieces with simple tubes passing directly to the ear on the same side, as shown in Fig. 1 *A*. Hantschmann and Nicolai[4] reported that this instrument was of value in the study of cardiac and pulmonary disease.

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Read before the American Heart Association, Section for the Study of Cardiac Diseases, at Atlantic City, N. J., June 8, 1937.

In 1935, Hawthorne[5] described the use of the differential (double) stethoscope, a type similar to the one described by Nicolai.[3] Alison[6] had described this type of stethoscope, in 1858, and gave a report on its use in 1859.

The symballophone, or sound-comparing stethoscope, which we have devised is illustrated in Fig. 1 *B*. The essential point of difference from Muralt's stethoscope is the introduction of a *longer connecting tube* from each endpiece to the *opposite* ear than the direct tube passing to the ear on the same side. The difference in length between the direct and crossed tubes is not a fixed distance; but we have found that if the crossed tubes are only 3 cm. longer than the direct

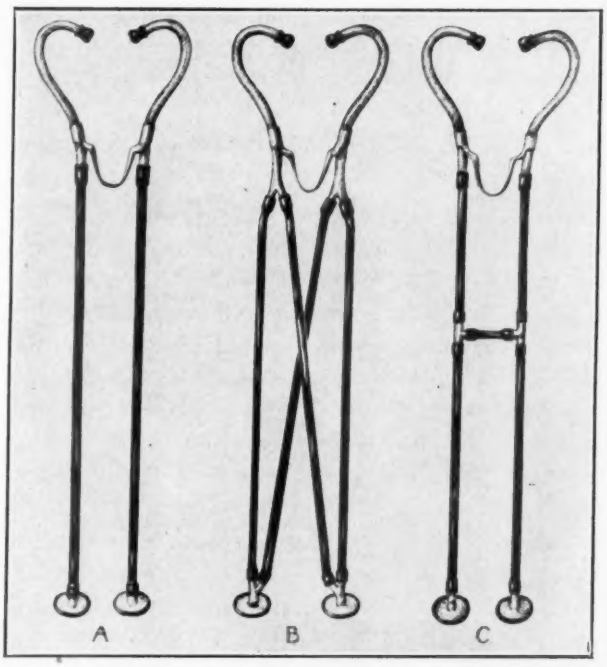

Fig. 1.—*A*, Nicolai's stethoscope; *B*, the symballophone showing the arrangement of tubing for a simple model. The diagonal tubes are longer than the lateral tubes, and the bore of the crossed tubes is reduced. *C*, a variation of *B*, but impractical.

tubes the device will serve its purpose. If the crossed tubes are about 15 to 20 cm. longer than the direct tube, the lateral deflection of the point of origin of the sound appears to be maximal. If the caliber of the crossed tubes is less than that of the direct tubes, the difference in the intensity of the sound reaching the two ears further enhances the ability to *lateralize* the source of the sound. Empirically, if the crossed tubes have a bore three-fourths that of the direct tubes, the results are best. Further study is in progress to determine the optimal differences in caliber and lengths of tubing. Psychological studies show definitely that with the use of the symballophone dissimilar sounds arising from any two points to be compared give an illusion which seems to lateralize

the quality being investigated. If one endpiece of the instrument is used alone, the impression of lateralization is enhanced.

Modifications of the arrangement of tubes may be devised. Fig. 1 *C* shows one of these modifications which has a single connecting tube between the two direct tubes, each going from the endpiece to the ear on the same side. The connecting or crossed tube permits sound waves to pass in either direction in going to the opposite ear, and if the length of the crossed tube is approximately 3 cm., the comparison of sounds may be made to permit lateralization. However, confusion may arise because sound waves may travel readily up or down the direct or vertical tubes. Refinements may be added to eliminate the long or diagonal tubes shown in Fig. 1 *B*. Stopcocks may be inserted near the endpieces for this purpose. If the two endpieces are then placed in juxtaposition over the heart or lungs, the instrument will serve as a familiar binaural stethoscope.

The theoretical basis for the construction of the comparing stethoscope may be stated briefly as follows:

Sound travels in air at the rate of 330 meters per second or 3.3 cm. per 1/10000 second. The rate in sea water is approximately 1454 meters per second or 14.5 cm. per 1/10000 second. The rates for solids vary from 3000 to 5000 meters per second. The auditory apparatus is capable of detecting very small differences in time of reception of sounds. Sounds which arrive 0.000032 second apart can be perceived. If the crossed or diagonal tubes shown in Fig. 1 *B* are 3 cm. longer than the straight or direct tubes, any sound traveling by air at the rate of 330 meters per second and originating at one of the endpieces will reach the homologous ear through the straight or direct tube 0.0001 second before it reaches the opposite ear. This difference in the time of reception in the two ears is three times the minimum time necessary for differentiation and will create the impression that the sound arose from the side which registered the sound first. From our observations, sounds originating in the blood stream heard at one endpiece and passing to both ears (in different times) register before those received at the other endpiece reach the ears. Theoretically, this should not be possible if the sounds heard are propagated from their points of origin in a fluid or solid medium. In the practical use of the comparing stethoscope, it is apparent that the sounds heard over vessels (murmurs) travel at a rate approximating the rate of travel of the pulse wave and not at the rate at which sound would travel through a liquid or solid medium. Clinicians will appreciate the fact that the systolic thrill over the carotid arteries in aortic stenosis is simultaneous with the systolic murmur at that point, and that the thrill is simultaneous with the pulse wave which is approximately one-twentieth of a second after the contraction of the ventricles. It is probable that the murmurs heard along their path of propagation are produced by vibrations in the blood or walls of the

vessels associated with eddies in the blood which are continued for a considerable distance beyond the point where faults in streamlining initiate them. Further studies with accurate registration of the propagation of sound impulses are being made.

Tests for the practical use of the instrument have shown that localization of the side from which the sound appears first is readily determined. Among a class of 50 senior medical students, no errors were made. In addition to the ability to detect differences in timing, differences in pitch and intensity can be appreciated by the quick comparison made possible by this device.

It is suggested that this instrument will also be of use in studying the following conditions: injury of one recurrent laryngeal nerve; unequal volume and timing of pulsations in peripheral arteries; asynchronous beating of the heart of twins in utero; unequal contractions of muscles; peristaltic sounds in the large intestine; and possibly in other clinical conditions where differences in timing and intensity of sounds are observed.

The device should be of great practical value in comparing sounds associated with respiration over two sides of the chest. Differences in timing, pitch, and intensity are easily detected, and the location of râles, friction sounds, and other abnormal sounds are readily localized.

By the use of the comparing stethoscope, the interest of the clinician in sounds is quickened. Sounds may be said to take direction and to be "alive." To listen over a vessel in which the blood is flowing and carrying vibrations which we interpret as sound, conveys a sensation of fluid in motion which is not produced by listening to the murmur with the familiar binaural stethoscope.

The illusion which is created by the devices of increasing the length and decreasing the bore of tubes passing to the opposite ears from two endpieces is of value in clinical medicine and in other fields where a comparison of sounds is desirable. One may compare two areas for compound differences in qualities which may be analyzed separately. The direction in which sound is traveling can be determined. This is of practical importance in the case of murmurs.

Further psychological studies are in progress. No permanent model can be constructed until all the facts are known. From an empirical standpoint, the device marks a signal advance among the aids in clinical diagnosis.

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A QUANTITATIVE STUDY OF CUTANEOUS CAPILLARIES IN HYPERTHYROIDISM*

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THE cutaneous circulation, in addition to serving the function of local tissue metabolism, assists in the dispersion of heat from the body. Disturbance of the cutaneous circulation is, therefore, to be expected in conditions that alter the total metabolism. This correlation occurs in fever. It may be expected in hyperthyroidism, but we have found no quantitative demonstration of its occurrence in this condition.

By capillary microscopy, first described by Lombard,[1] it is possible to study directly some of the vessels of the skin. The following calculation, based upon figures obtained from the dorsum of the hand, indicates how few of these vessels are visible. The length of a capillary loop approaches 0.82 mm. and its width 0.008 mm. The total number of visible loops per square cm. is approximately 8,100. Hence the visible capillaries per square cm. would contain 0.334 c.mm. of blood. As the surface area of a man of 80 kgm. is approximately 1.8 sq. meters, such a man would have, assuming the same capillary distribution, about 6 c.c. of blood in his visible capillaries. In addition, the subpapillary venous plexus is more or less visible. On the average, the individual limbs are 0.03 mm. wide and approximate an arrangement of superimposed circles with centers 0.3 mm. apart. By a similar calculation, the total amount of blood contained in the subpapillary venous plexus of the entire body would be about 16.9 c.c., making a total for the visible vessels of the skin approaching 22.9 c.c. These figures are subject to correction for variation in size and distribution of the vessels in different skin areas. We found that vessels of the subpapillary plexus over the face and neck are distinctly wider and the total number of capillaries per sq. cm. distinctly greater than the averages given here. The vessels of the plexus over the trunk are narrower and the distribution scantier. In spite of these observed variations the approximation is useful until better figures are available.

That this amount of blood is sufficient to account for the color of the skin may be shown by the following procedure: From the above figures the amount of blood in one sq. cm. of skin is found to be about 1.3 c.mm. To each of two glass cylinders, having an area at the base of 15.9 sq. cm., were added 2 c.c. of distilled water. One of these cylinders was placed over the skin and the skin color observed through a peephole. The color

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exactly matched that of the surrounding skin. Pressure was applied by the cylinder to the skin and the skin blanched.

To the second cylinder 20 c.mm. of whole blood were added. (We estimated 1.3 c.mm. of blood per sq. cm. of skin. As the base of the cylinder was 15.9 sq. cm. a similar area of skin would contain 20.67 c.mm. of blood. The contents of the cylinder were then comparable to the amount of blood in the visible vessels.) With this container the above procedure was repeated as with the cylinder containing only distilled water. Seen through the peephole the skin was definitely darker than the surrounding skin. When pressure was applied the color matched that of the surrounding skin.

The visible circulation is therefore adequate to explain the color of the skin but we believe it inadequate to account for the heat loss occurring from the skin. However, this visible circulation shows alterations which are probably typical of those occurring in the entire cutaneous circulation.

Four different kinds of observations could be made to study these changes: (1) speed of flow; (2) per cent of total capillaries showing flow; (3) width of vessels; (4) number of capillaries normally open as compared with the total number open in the same area under conditions of maximal dilatation. This fourth method we considered would supply quantitative data with a minimum of subjective error, and was therefore the one chosen.

Most observers who, in capillary microscopy, have used the dorsum of the hand have found little change in the number of capillaries under varying experimental conditions. Lewis[2] indeed states that all the capillaries in this area are constantly open. Bordley,[3] on the other hand, finds a varying change in the number of open capillaries in the skin over the tibia. We have found that on the face, neck, and hands in exposed areas most or all of the capillaries are open constantly, but over the arms and other areas protected by clothing that only a fraction of the total number are open.

METHOD

Patients with hyperthyroidism were obtained from the endocrine clinic or from the wards of the University Hospital. All had a definite diagnosis of hyperthyroidism and an elevated basal metabolic rate without subsequent treatment preceding our study. As controls we used patients from the wards or dispensaries in whom no vascular nor metabolic disturbance could be found. All cases when studied had been in the hospital at least two hours. A thyroid case and a control were examined alternately throughout the study, which was started November, 1936, and completed May, 1937.

The skin area studied was on the forearm, midway between the wrist and the elbow. The arm was placed at the level of the sternum. An area of approximately 2 sq. mm. was marked by inking a circular die and

pressing it gently on the skin. The exact area varied somewhat with the tension and elasticity of the skin and the tendency of the ink to run slightly, but when once marked was constant for the duration of the experiment.

The method of capillary microscopy was that previously described by one of us.[4] The area was covered with cedar oil. Light from a 500-watt bulb was cooled by passing it through water and directed upon the area. Observations were made using a microscope with a magnification of ×32. The number of visible capillaries was recorded.

At a distance of 1 cm. from the marked circle histamine 1:1,000 was pricked into the skin and, at one-minute intervals, the number of visible capillaries was counted. The maximum number was recorded.

RESULTS

Sixteen cases of hyperthyroidism are reported, with fourteen controls. Before histamine is pricked into the neighboring skin a number of capillaries can be counted. Because the capillaries pass almost at right angles to the skin surface only their tips are visible, appearing as small loops or hooks. In the patient with hyperthyroidism many more capillaries can be seen than in the control, as a rule. After histamine there is a striking increase in the number of visible capillaries in the control. After histamine in the patient with hyperthyroidism there is a relatively slight increase in the number of visible capillaries. It is obvious that the increase after histamine is marked in the control and negligible in the patient with hyperthyroidism. It is to be noted, however, that the patient with hyperthyroidism has a large number of capillaries visible before histamine.

The change in the number of visible capillaries in a normal subject before and after histamine is illustrated in Fig. 1. Photographs were made using an Ultrapak, Leitz camera, and arc lamp. The exposure was one second. The intensity of light was identical for both exposures. In the first film only two capillaries show as tiny black dots close to the free end of the upper hair. At this low magnification the capillary tips show as dots. The general field is quite light. The stubs of two hairs show. The ink marking has been trimmed away in the photograph except for a small dab of ink which has run along the roots of the hairs. The second photograph was taken four minutes after histamine. Macroscopically the marked circle lies in the flare area. In the photograph the entire field is much darker. The two capillaries previously seen are still present and many others have appeared. Short lengths of the subpapillary venous plexus are visible. In a photograph made at a single focus their continuity with each other cannot be demonstrated. Similarly, all capillaries are not in focus and absolute counts cannot be made from photographs. The lower hair has been swept out of the field and the upper is bent slightly downward and is more clearly in focus.

The results of the entire series are charted in Fig. 2. The increase averages 120 per cent for the controls, with a range of 62 to 220 per cent. For the patients with hyperthyroidism the average increase is 16 per cent with a range of 0 to 82 per cent. The patient designated

Fig. 1.—Photomicrographs taken of the extensor surface of the forearm in a normal subject. Area of approximately 2 sq. mm. The photomicrograph on the left shows the normal appearance. Only two capillaries are visible as dots near the free end of the upper hair. The photomicrograph on the right shows the same area after histamine. Numerous capillaries and branches of the subpapillary venous plexus are visible and the entire field is darker. For further details see text.

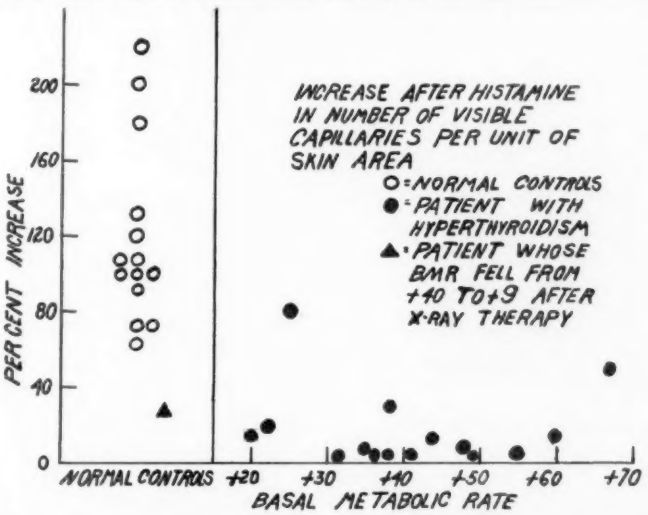

Fig. 2.—Chart showing the relation between basal metabolic rate and per cent increase in capillary counts after histamine in normal controls and in hyperthyroid subjects.

by a triangle is not included in the series. She was a patient, formerly hyperthyroid, whose basal metabolic rate had fallen to normal following roentgen treatment but who retained the capillary behavior similar to that which we found in hyperthyroid patients.

The capillary counts are not given because (1) for reasons previously stated the size of the area studied was not exactly the same in different

patients and (2) conditions of skin texture affect visibility and hence the count. In the controls before histamine the average count was 16, ranging from 8 to 24, while in the patients with hyperthyroidism the average was 23, with a range from 8 to 42.

DISCUSSION

The volume of blood in the visible vessels is too small to be important in heat loss. If, however, these vessels reflect the behavior of all the minute vessels of the skin, of which they form a part, then their behavior becomes significant. The evidence presented suggests that in the hyperthyroid state most of the cutaneous capillaries are open, as might be expected to provide for the heat loss. Such increased filling of the peripheral bed, if unaccompanied by constriction elsewhere, would necessitate an increase in blood volume. Chang[5] has reported an increase in blood volume in hyperthyroid states.

The degree of cutaneous dilatation is not closely correlated with the basal metabolic rate, for patients with minimal change of capillary count in response to histamine had basal metabolic rates ranging from plus 32 to plus 55, whereas two patients with the highest basal metabolic rates (plus 60 or over) had increased counts after histamine in one case by 50 per cent and in the other by 16 per cent. This is in accord with the findings on blood volume, for the increase of the basal metabolic rate is reported as not proportional to the increase in the blood volume.

SUMMARY

Capillary counts were made in an area of approximately 2 sq. mm. in normal controls and in hyperthyroid patients. The area chosen was the extensor surface of the forearm midway between the elbow and wrist. Capillary counts were made in the same area before and after pricking histamine into the skin. While absolute counts in different patients cannot be directly compared, per cent increase in the same patient is considered significant. Of the sixteen hyperthyroid patients, the increase averaged 16 per cent, of the fourteen controls, 120 per cent.

It is suggested that in the hyperthyroid state an increased dilatation of the cutaneous circulation assists in the loss of heat by the body. The degree of dilatation is not related quantitatively to the height of the basal metabolic rate, however.

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THE TREATMENT OF SCLERODERMA BY MEANS OF ACETYL BETA METHYL CHOLINE CHLORIDE (MECHOLYL) IONTOPHORESIS*

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THE object of this report is the presentation of a new method of treatment of the condition commonly known as scleroderma. A survey of the literature makes it apparent that this is a diagnostic term which is rather loosely used. European writers for the most part describe scleroderma verum as a disease primarily involving the torso and proximal parts of the extremities. Acrosclerosis is the term applied to a condition manifesting similar skin changes but primarily affecting the distal parts of the extremities and always associated with vasomotor disturbances. Sellei[1] attempted in 1934 to differentiate between these two conditions. In this country the term scleroderma is customarily used to include both processes. Brown, O'Leary, and Adson[2, 3] in their reports of 1930 group their cases of acrosclerosis under this heading.

Sellei believes that the true scleroderma, as he classifies it, has a definite etiology in deficient pancreatic function and he reports almost 100 per cent success in treating these cases over a period of two years with extracts of pancreas, muscle, and liver. Other writers[4-10] in discussing treatment usually refer to those cases in which a vasomotor disturbance is present and more than one-half of the recommended therapy is based on an attempt to improve the circulation to the skin. The arterial sympathectomy of Leriche and the ramisection and ganglionectomy of Brown and Adson are attempts in this direction. Another group of workers have approached this problem from the viewpoint of possible endocrine pathology and consider that the vasomotor disturbances and the calcium imbalance which are present are due to dysfunction of the adrenal, pituitary, thyroid, or parathyroid glands. Bernheim and Garlock,[11] and Leriche and Jung[9, 10] have reported some success following partial parathyroidectomy. Osler[12] reported a series of eight cases improved by the use of thyroid extract and one of the authors of this paper has seen a case improve during the use of anterior pituitary therapy.

It is apparent that since success has been reported following these various forms of therapy in all probability the cases treated had different etiologic backgrounds and it may be proven in the future that the pathologic condition of which we are speaking is a syndrome pos-

Read before The American Heart Association, Section for the Study of the Peripheral Circulation, at Atlantic City, N. J., June 7, 1937.

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sibly resulting from several causes. In the experience of the authors, however, improvement with any previous treatment has been rare. None of the patients reported in this paper had shown even moderate improvement prior to their appearance, although their treatment included a wide variety of therapy such as noted below.

We shall not attempt in this paper to discuss the possible mechanisms involved in the production of this syndrome. The field has been admirably covered by Lewis and Landis[13] and more recently by Prinzmetal.[14] They have demonstrated the circulatory mechanics involved in scleroderma. Removal of the sympathetic control of the peripheral circulation by surgery in cases of a Raynaud's syndrome without scleroderma results in the release of spasm and an abundant blood supply. If scleroderma has produced a mechanical blocking of the vessels due to the tension of the leathery skin, vasodilatation by removal of sympathetic control is impossible.

It has been our experience that the relief of spasm by mecholyl iontophoresis in Raynaud's disease without scleroderma has been of only temporary value. However, as reported in this paper, in scleroderma there appears to be a softening of the thickened skin as well as a vasodilatation.

We are reporting herein a series of thirty-four patients with scleroderma who have been studied by the staff of the Vascular Clinic at the New York Post-Graduate Hospital. Of these all but one are patients with vasomotor disturbances and therefore should be classified according to Sellei as acrosclerosis. The first patient in this series was seen in April, 1933, and the majority of the patients were followed throughout 1935 and 1936. Table I shows the distribution of these cases as to age,

TABLE I

SCLERODERMA IN 34 PATIENTS

AGE	Eight years to 61—Average—37.9 years
SEX	Eight males, (23.5 per cent)—26 females, (76.5 per cent)
BIRTHPLACE	America—25
	Russia—3
	Italy—3
	Germany—3
DURATION OF SCLERODERMA	Three months to 180 months—Average—59.3 months
COMPLICATING RAYNAUD'S	32 definite—2 doubtful
AVERAGE DEGREE OF DISABILITY	Av. ++ to +++
	Range (+ slight to ++++ complete)
BLOOD PRESSURE	90/? to 164/92

sex, nationality, duration of the illness, and the average degree of disability. Twenty-six (76.5 per cent) were in females, and this corresponds to the sexual ratio of Raynaud's syndrome. The average age of the patients treated was 37.9 years, the extremes were eight and sixty-one years. This approximates the usual age incidence of vasospastic

diseases. The average duration of the history of sclerodermal changes was 59.3 months, the extremes were nine months and fifteen years. Occupation apparently had little or nothing to do with the etiology. Hands were much more frequently involved than feet and disability ranged from total incapacity for activity to a slight stiffness of the fingers. Capillary examinations in most individuals in which the skin changes permitted visualization of the vessels, showed large dilated loops typical of a Raynaud's syndrome. Seventeen of the patients had developed trophic ulcers. None had gangrene involving more than two square centimeters of surface area.

The use of various choline derivatives, especially acetyl beta methyl choline chloride (mecholyl*) in the treatment of certain peripheral vascular diseases including preliminary data dealing with scleroderma, has been previously reported from our clinic.[15, 16, 17] It was noted that in some patients there was a definite softening of the thickened skin following the prolonged use of this substance by iontophoresis. This drug is absorbed if used in the form of a solution on a bandage over the affected areas to which is applied the positive electrode of a galvanic battery. Sufficient of the choline (whether changed or unchanged) may be absorbed to produce systemic reactions during the course of the treatment, such as sweating, increased salivation, a drop in blood pressure, and frequently increased intestinal peristalsis. In the treatments reported in this study a one-half of one per cent solution of the drug was applied to the asbestos bandages, and about twenty milliamperes of current were allowed to flow for twenty to thirty minutes during each treatment. Locally a marked vasodilatation occurs so that after the removal of the bandage an area of rubor persists for several hours which is accompanied by sweating.

The technique has been described in detail in the above references.[15-17] One observation is worthy of note. The negative electrode is usually placed on the back of the patient. This pad is well moistened with tap water and is applied firmly to the body. Among the patients with scleroderma slight negative burns were frequently noted; while in treating patients for other conditions they seldom occurred. It would seem that the skin of the former group is more sensitive.

An attempt was made to treat parts showing marked changes in the skin typical of the pathologic condition. Because of technical difficulties certain areas on the face, neck, and trunk were left untreated. It was impossible to treat extensive lesions at one time and in patients having large areas involved more frequent treatments were given. The solution was applied to not more than two extremities on one day. Daily applications were given in as many cases as possible but the majority of our patients received treatment two or three times a week.

*The acetyl beta methyl choline chloride (mecholyl) used in this study was supplied through the kindness of Merck & Co., Inc., Rahway, N. J.

These patients have received from 6 to 165 treatments. Little, if any, results were noted with less than 10 treatments. Some patients stopped after 30 or 40 treatments because the degree of improvement was satisfactory. It would seem from our observations that probably 50 treatments would be necessary in most instances and in the advanced forms of the disease many more before a satisfactory result can be obtained.

Patients in our series had previously received many forms of treatment with little or no success. Case 21, showing marked improvement with mecholyl iontophoresis, had had a parathyroidectomy and a unilateral thyroidectomy a year previously with very slight improvement. Cortical extract administered for two years had also been ineffectual. Case 23 had had a bicervical sympathectomy, triple typhoid vaccine, tissue extract, and glycine without results. It was interesting to note that she had been given ergot in spite of the fact that she had a Raynaud's syndrome. She was skin-sensitive to mecholyl and therefore this form of therapy could not be used. Case 26 also received ergot. In addition she was treated with intravenous sodium citrate, typhoid vaccine and diathermy, and a sympathectomy. Two cases died cardiac deaths before sufficient therapy could be administered. One had mitral stenosis and was fibrillating, and the other had arteriosclerotic heart disease. One other patient (Case 18) in our series died from Addison's disease before any treatment was instituted for the scleroderma. Two of our patients showing a pronounced Raynaud's syndrome and excessive arsenic secretion in the urine were given a diet low in arsenic and injections of sodium thiosulfate without improvement of the scleroderma. One of these patients has just started mecholyl treatment. The other has received over 100 treatments with very marked improvement (Case 19).

Our criteria for classifying patients as "markedly improved" are as follows: 1. Restoration of practically normal function. 2. Healing of existing ulcers. 3. Softening and loosening of the skin. 4. Return of sweating and hair to the affected areas. 5. Increased visibility of capillaries (not always noted).

TABLE II

RESULTS OF MECHOLYL IONTOPHORESIS TREATMENT OF 27 PATIENTS WITH SCLERODERMA

IMPROVEMENT	NUMBER OF TREATMENTS	REMARKS
Marked—9 patients	33 to 165 Average 81.0	No other form of therapy
Moderate—7 patients	10 to 88 Average 32.0	2 received tissue Extract No. 568 1 died pneumonia
Total improved—16 patients		
Slight or none—11 patients	6 to 20 Average 11.8	1 atypical 1 result unknown 1 by mouth

Patients classified as "moderately improved" have shown a definite approach toward the above listed criteria. Those showing only slight response to therapy have been included in the unimproved group. Table II summarizes the results of treatment. All cases receiving 30 or more treatments showed either marked or moderate improvement. Cases showing no improvement were noted to have received 20 or fewer treatments. An atypical case did not respond to this form of therapy.

The following two typical cases of scleroderma are briefly summarized. They both showed marked improvement to mecholyl iontophoresis.

PATIENT L. C.—*Present Illness:* A female, aged fifty years of Italian parentage, was first seen on March 3, 1934. She had complained of stiff and painful fingers and toes for five years with inability to do any form of work. After exposure to cold they would turn blue and become painful. This would disappear after five to ten minutes in a warm room. During the last two years the skin of the face had become stiff and motion of the jaws was limited.

Past History.—There was no illness. She had had three normal pregnancies. Menopause had occurred six months before her first clinic visit. She has eaten 1½ pounds of rye bread daily for years.

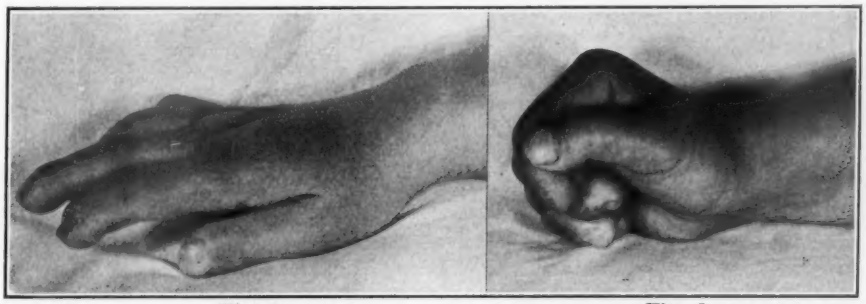

Fig. 1. Fig. 2.

Fig. 1.—Patient L. C., maximum finger flexion before treatment. Marked trophic changes are present.

Fig. 2.—Patient L. C., maximum finger flexion after 170 treatments with mecholyl iontophoresis.

Physical Examination.—The patient was a well-nourished, slightly obese Italian woman appearing about her stated age. The face was expressionless and wax-like. The nose was pinched and the upper lip almost immobile. The fingers were stubbed, the distal phalanges being shortened. Motion in all finger joints was nearly zero. Trophic changes were present over the tips of the fingers and the nails were markedly deformed. No ulcers were present when she was first examined. The toes showed slight changes of a similar nature. The skin was very tense and felt like leather.

Capillary Microscopy.—The vessels were seen with difficulty, and were reduced in number. There were no dilated loops. There was a moderate rate of blood flow. The complete physical examination and routine laboratory tests were normal.

Treatment.—Nineteen injections of acetyl choline 100 mg. each were given in five months with very slight improvement. From September, 1934 to May, 1937, she was given 170 treatments of mecholyl iontophoresis. Improvement was marked. The patient could smile. Fingers could be flexed to almost a complete fist and she could do all of her household work. Some pain persisted, especially at the calcinosis area over the middle joint of the fourth right finger. Deformities were still present.

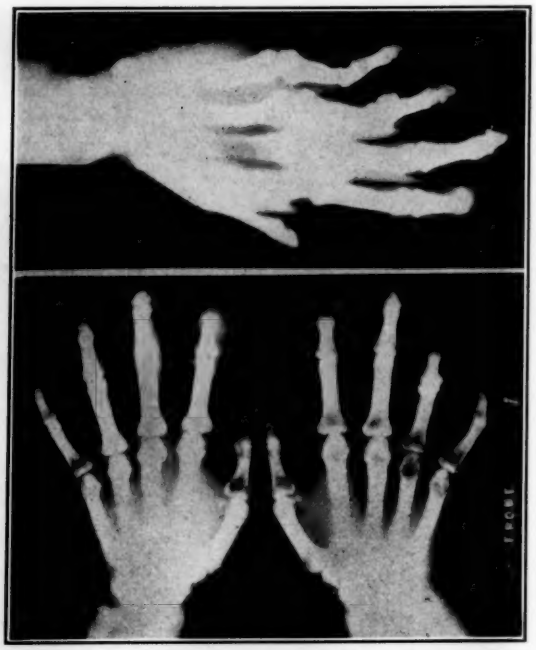

Fig. 3.—Patient L. C., x-ray films of the right hand showing atrophy of the terminal phalanges and calcinosis of the middle metacarpal joint of the fourth finger.

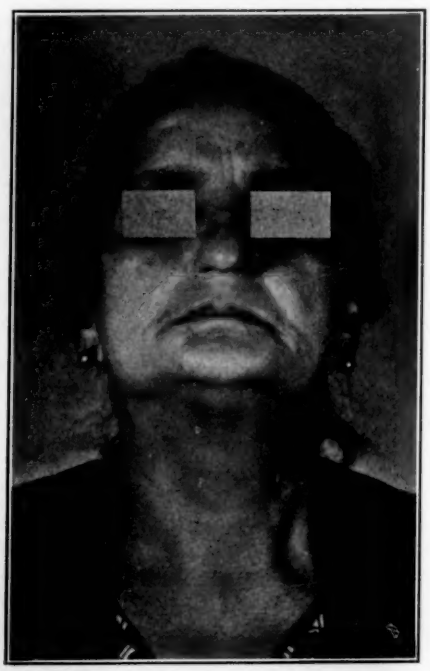

Fig. 4.—Patient L. C., masklike expression of the face due to the thickened skin.

PATIENT C. D.—*Present Illness:* The patient, aged fifteen years, American born of Italian parents, was first seen on May 12, 1936. She was transferred from another hospital where she had been treated for a hyperchromic anemia with accompanying symptoms of weakness and exhaustion. Fifteen months before she was seen by our clinic there developed stiffness of the skin of the hands, arms, and neck. Arsenic was found in excess in the urine and following sodium thiosulfate, 0.5 gm. three times a day by mouth, there was a marked improvement in the blood count.

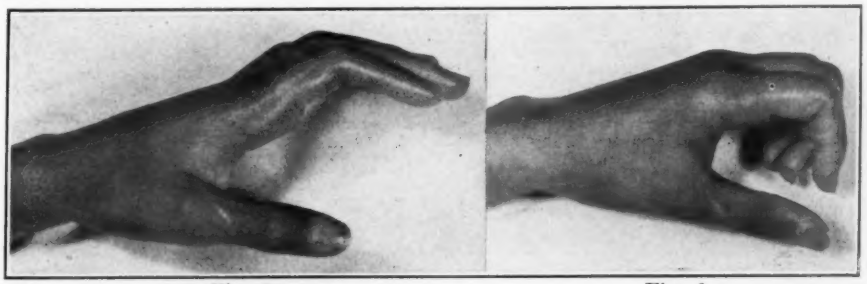

Fig. 5. Fig. 6.

Fig. 5.—Patient C. D., maximum flexion of fingers before treatment.

Fig. 6.—Patient C. D., maximum flexion of fingers after 128 treatments with mecholyl iontophoresis.

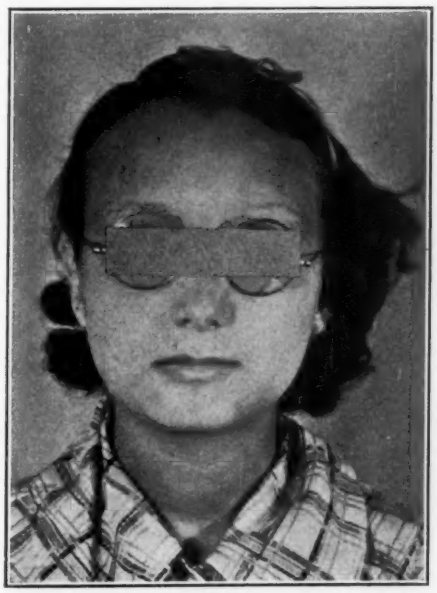

Fig. 7.—Patient C. D., Note the pinched expression and the waxy character of the facial skin.

It rose from 2.3 millions on Oct. 27, 1935 to 5.1 millions on Dec. 17, 1935. The sclerodermal changes however increased until, when she was seen in our clinic, they were incapacitating. She could not hold anything with her hands and was unable to dress herself. Cold aggravated her symptoms and induced cyanosis.

Past History.—Essentially normal.

Physical Examination.—The patient was a fairly well-nourished and mentally alert girl of fifteen years of age. The blood pressure was 110/80; pulse, 72; all

other findings likewise normal except for thickened leathery skin over the face, neck, and hands. There were trophic changes over the knuckles and tips of the fingers with a few tiny active ulcers. Fingers could be only very slightly bent.

Capillary Microscopy.—There were markedly dilated capillary loops with long periods of blood stasis.

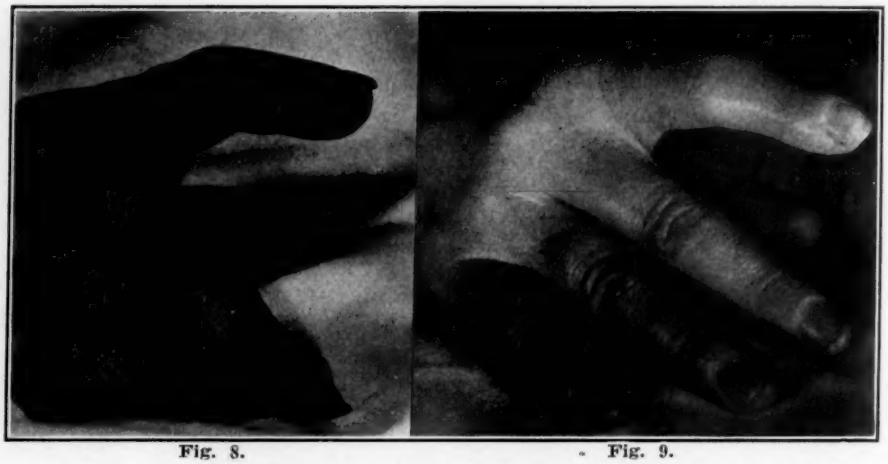

Fig. 8. Fig. 9.

Fig. 8.—Patient H. S., ulcer on the tip of the index finger complicating scleroderma.
Fig. 9.—Patient H. S., ulcer healed after 107 treatments with mecholyl iontophoresis. Good function is present. Note the shiny skin.

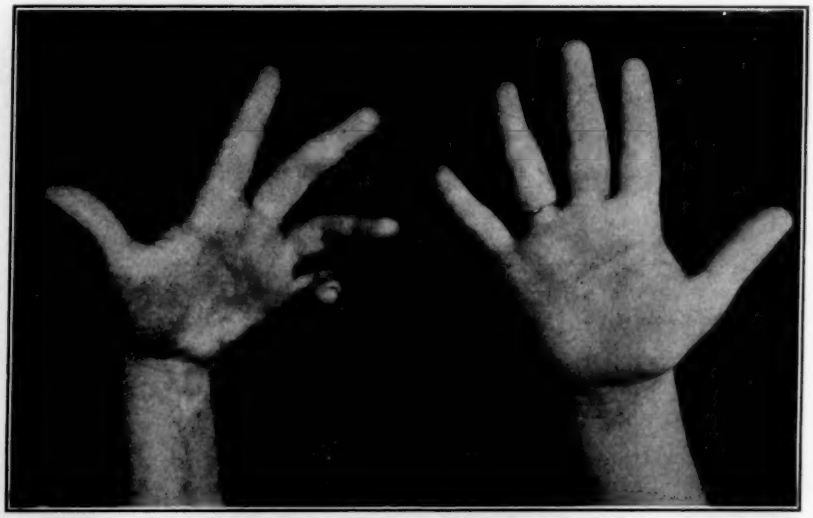

Fig. 10.—Patient M. T., scleroderma with atrophy. No Raynaud's syndrome is present. The hands show localized plaques. There was no improvement with mecholyl iontophoresis.

Treatment.—From May 18, 1936 until May 1, 1937 she received 128 treatments of mecholyl by iontophoresis with marked improvement. During cold weather in January, 1937 slight ulceration re-occurred over several phalangeal joints. At the termination of the treatments (May, 1937) motion was sufficient for her to carry on nearly all activities, including dressing. She could smile and open her mouth wide enough to eat easily.

We believe that the usual need of an alternate case control series is not a requisite in this study for the following reasons. First, these

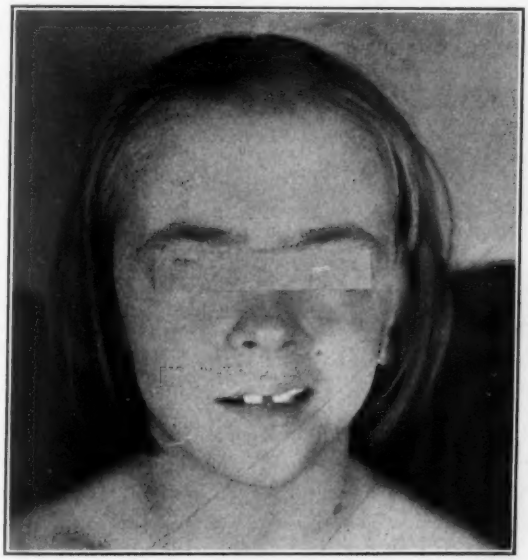

Fig. 11.—Patient M. T., scleroderma with atrophy. Face deformed by a lesion on the left cheek.

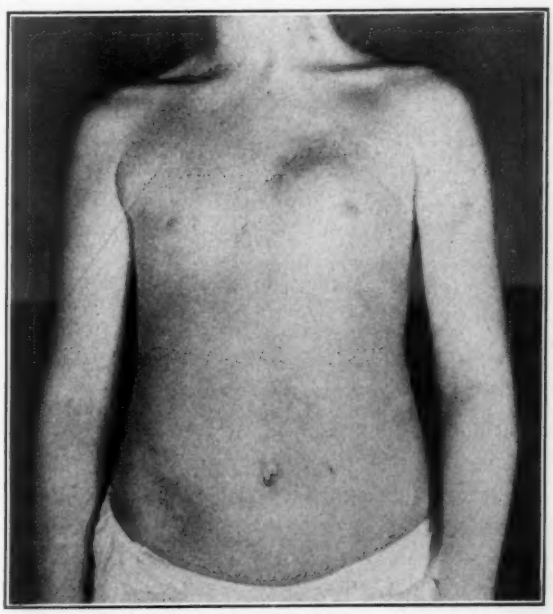

Fig. 12.—Patient M. T., scleroderma with atrophy. Isolated plaques on the chest and abdomen.

patients do not tend to have spontaneous cures and a number of them had received previous treatment of many types without results. Second, the psychic factor can be ruled out by the failure of previous elaborate

therapy, such as operative procedures. Third, previous studies with galvanism, using water or saline, failed to show improved circulation. Fourth, results from ganglionectomy are local and limited to the operated extremity, while mecholyl iontophoresis has shown softening of untreated areas.

COMMENT

Many of the patients in our series are still under treatment and it is likely on the basis of past experience that the list of those "markedly improved" will be somewhat larger as further treatments are given. It should be noted that the improvement is not confined to the areas treated but is observed in all areas affected by the scleroderma. There has been a tendency in several of the patients to have slight relapses; in each instance produced by some factor aggravating the Raynaud's syndrome such as cold, emotion, or trauma. It is probable that some serious relapses will occur. Several of the early treated cases have maintained their improvement without treatment. Case 1, having received eighty-five treatments, has maintained a satisfactory condition although his last therapy was given on March 18, 1936. Case 10, after 34 treatments showed marked improvement, and this has been maintained without further treatment since 1935. Many studies concerning both the disease and the treatment remain to be carried out. Blood calcium studies were done on some of the patients and for the most part showed normal figures. It is realized, however, that such figures are of very slight significance and that calcium balance studies over a long period should be undertaken in certain of these patients. Studies for arsenic in the urine were done on many of the patients. Those showing excess amounts were given a low arsenic containing diet and sodium thiosulfate intravenously without improvement. The endocrine studies were incomplete and we feel that in a careful case work-up these should be done in detail. There seems to be no connection between the use of tobacco and scleroderma, while the use of ergot may apparently aggravate the disease.

We appreciate the obvious disadvantages of this form of therapy with its technical difficulties. For the past four and one-half years we have been endeavoring without success to utilize the choline derivatives by other methods of administration.[15] Intravenously mecholyl is exceedingly dangerous and its effects fleeting. Subcutaneously it is also not without danger and its effects are short lived. Intranasally the risk is definitely lessened but the effects are still too brief.[20] Orally large and expensive doses are required. The effects are more prolonged but frequently gastrointestinal disturbances prohibit its use. Iontophoresis has advantages in that the maximum concentration of the drug may be obtained at the area most involved and that the action is prolonged over a period of four to eight hours or longer. It should not be used in any form without available atropin. The injection of $\frac{1}{150}$ of a grain of atropin sulfate will produce a cessation of the mecholyl effects.

CONCLUSION

A form of treatment has been presented for patients suffering from scleroderma which has given encouraging results in those receiving sufficient therapy. No other form of therapy of which we have knowledge has produced as satisfactory results. It would appear that the improvement is due to an increased vascularity in the affected parts, and a softening of the thickened dermis as a result of vasodilatation produced by acetyl beta methyl choline chloride, given by the method of iontophoresis.

Due acknowledgment is made for the technical assistance of Ellen McDevitt, B.S., and Elizabeth MacLenathen, A.B.

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FAINTING ATTACKS RESULTING FROM HYPERSENSITIVE CAROTID SINUS REFLEXES*†

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ROCHESTER, MINN.

THERE is hardly a condition in the field of medicine that disturbs a patient or affects his general morale as much as does the loss of consciousness or a severe attack of vertigo. Loss of consciousness, which is the result of various causes, is a relatively common occurrence. In the past it has been the custom to diagnose a large portion of attacks of unconsciousness as atypical forms of idiopathic epilepsy or simply to

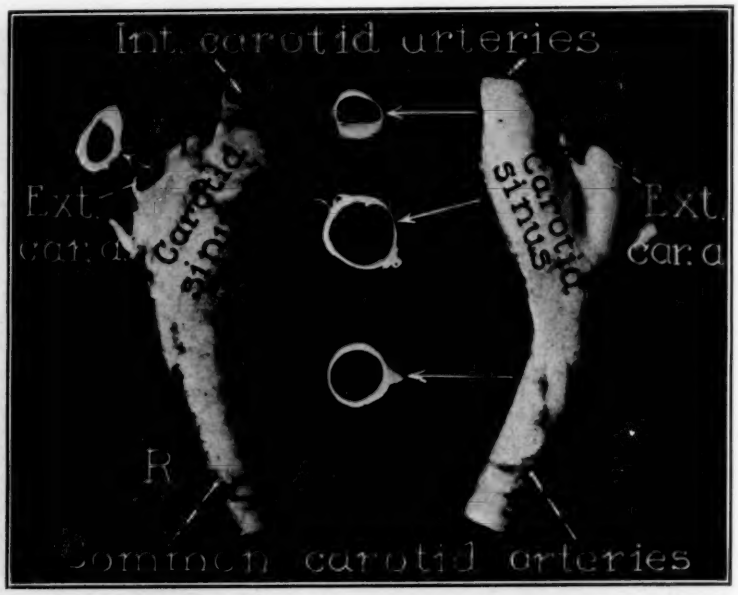

Fig. 1.—Anterior and posterior views of the right common carotid artery at its bifurcation into the external and internal carotid arteries; the carotid sinus appears in the first portion of the internal carotid artery as a bulbous dilatation.

group them under the general heading of "unconscious attacks." Just a few years ago unconscious spells due to hyperinsulinism were grouped under this general heading. Now, there is sufficient knowledge of another type of unconscious attacks to permit it to be classified as a definite clinical syndrome and to be separated from the general "unconscious attacks." This syndrome is characterized by spontaneous attacks of unconsciousness and vertigo and may or may not be associated with

*From The Section on Cardiology, The Mayo Clinic.
†Read before the meeting of the American Heart Association, Section on Cardiac Disorders, at Atlantic City, N. J., June 8, 1937.

mild convulsions due to hypersensitive carotid sinus reflexes. The attacks may be induced by making graded pressure over one of the carotid sinuses.

ANATOMY OF THE CAROTID SINUS

In man and in many animals the carotid sinus is a bulbous dilatation of the first portion of the internal carotid artery[1] (Fig. 1). The wall

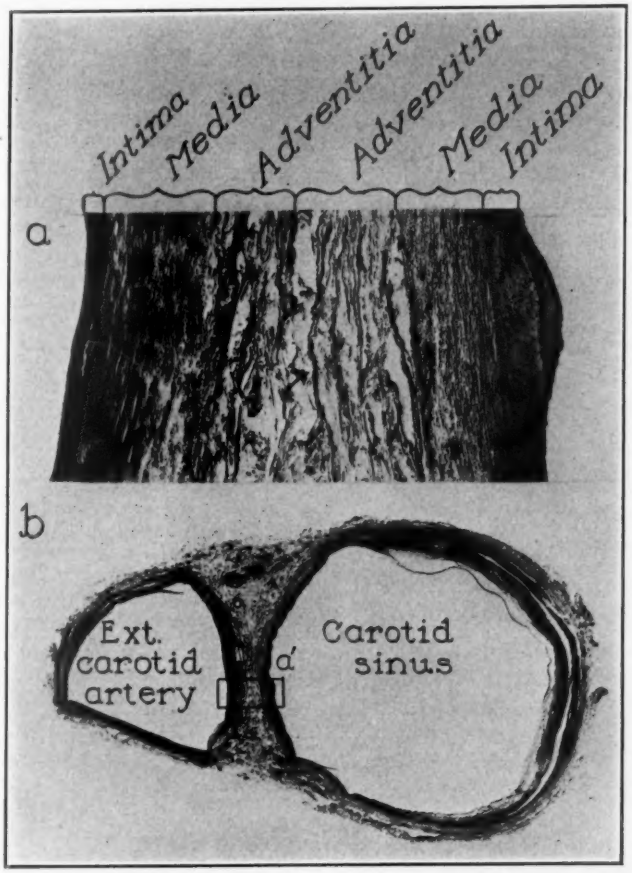

Fig. 2.—*a*, Section taken *a'* in *b*, showing wall of external carotid artery and wall of the carotid sinus; the media of the wall of the external carotid artery is thicker than the media of the wall of the sinus; the adventitia of the sinus appears thicker than that of the external carotid artery; stained with hematoxylin and eosin (×75); *b*, section through the external carotid and the carotid sinus of a white woman aged fifty-five years; the carotid sinus is much larger than the external carotid artery at the same level; stained with hematoxylin and eosin (×7).

of the carotid sinus is somewhat thinner than the wall of other portions of the artery. In the sinus the intima is practically the same as the intima of the rest of the artery.[2] The media of the sinus is thinner and contains more elastic tissue and less muscular tissue than the media of the rest of the artery (Fig. 2). The adventitia of the sinus is thicker

than the adventitia of the rest of the artery and contains special nerve cells called nerve receptors.[3] These nerve receptors are situated between the layers of collagen.

Innervation.—Investigators are not entirely agreed as to the complete innervation of the carotid sinus,[2, 4] but most of the outstanding investigators agree that the carotid sinus is supplied with branches from the glossopharyngeal, vagus, and cervical sympathetic nerves and occasionally by a few branches from the hypoglossal nerve. The branch from the glossopharyngeal nerve is called the nerve of Hering.[5]

THE FUNCTION OF THE CAROTID SINUS

It has been proved by physiologists that mechanical or electric stimulation of the carotid sinus produces a combined reflex or cardiac inhibition and a fall in the systolic blood pressure, that is, the same effect that is produced by stimulating the central end of a depressor nerve.[6] It is believed that one of the functions of the carotid sinus reflex is concerned with the control of blood pressure, the heart rate, and the maintenance of an adequate circulation in the brain. It is thought by some investigators that an increase in pressure within the sinus will, by means of a reflex, cause a drop in blood pressure and a retardation of the cardiac rate and that a decrease in pressure within the sinus will increase the blood pressure, accelerate the cardiac rate, increase respirations, and increase the secretion of epinephrine.

I do not believe that all of the functions of the carotid sinus are fully known. There is not a satisfactory explanation as to why carotid sinuses in some instances become hypersensitive, but there is no doubt that they do.

ELECTROCARDIOGRAMS IN THE INDUCED ATTACKS

Stimulation of a sensitive carotid sinus induces striking changes in the cardiac conduction system.[7] The more important changes are sudden slowing of the heart rate, varying degrees of heart-block, and long periods of complete cardiac standstill (Fig. 3). In about half of the cases observed at the clinic the cardiac slowing was sufficient to cause the fainting attacks; in the other cases the slowing was absent or too slight to be of any significance.

RESPIRATIONS IN THE INDUCED ATTACKS

Stimulation of a sensitive carotid sinus by mechanical pressure produces rather marked changes in respiration. In the severe attacks the breathing becomes deep and labored (Fig. 4). There did not appear to be a constant correlation between the labored breathing and the cardiac slowing and the fainting attacks.

SYMPTOMS AND DIAGNOSIS

Carotid sinus syncope is much more common among males than among females. In the series of eighty-five cases observed at the clinic the ratio of males to females was 5:1. It is most common among middle-aged persons and elderly individuals and is rare among young persons. In this series of cases the oldest patient was seventy-eight and the young-

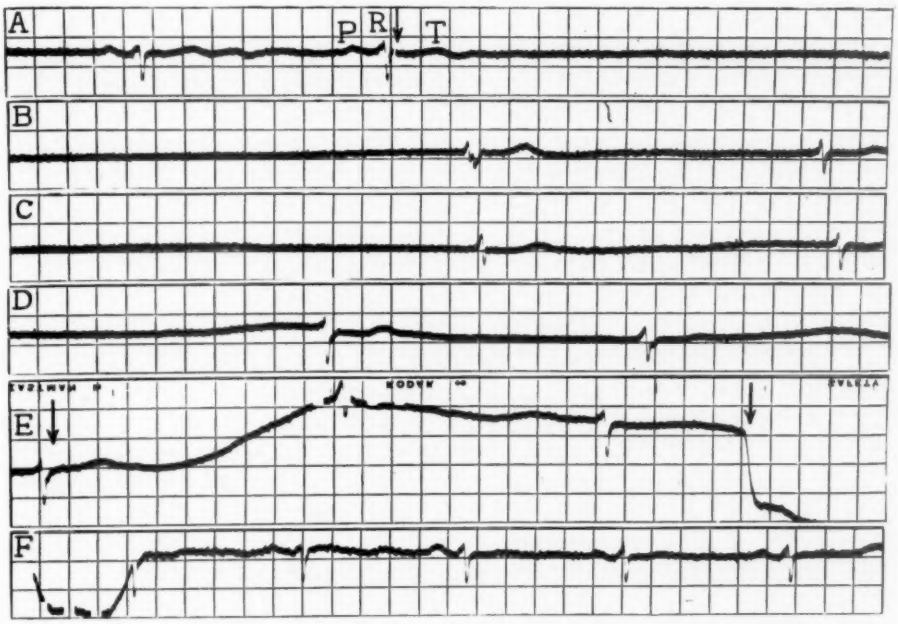

Fig. 3.—Electrocardiogram (Lead II) for a man aged fifty-nine years; *A*, *B*, *C*, *D*, *E*, and *F* represent continuous tracing; first arrow indicates beginning of pressure on the right carotid sinus; subsequently, cardiac standstill of 6.6 sec. with development of a convulsion at third arrow; idioventricular rhythm shown between first and last arrows.

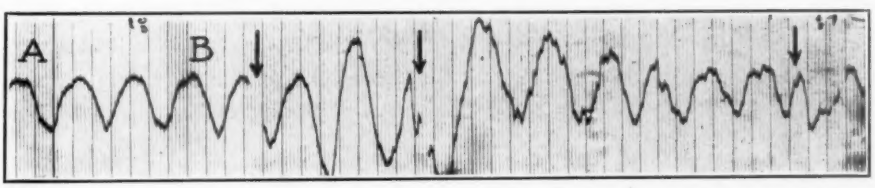

Fig. 4.—Respiratory response to carotid pressure in a man aged sixty-four years: *A* to *B* represents normal respirations; first arrow indicates pressure on the right carotid sinus; respirations became slower and deeper and patient became unconscious at second arrow and regained consciousness at third arrow.

est was twenty-eight years of age. The average age of the patients was fifty-six years. The chief symptoms were attacks of vertigo and spells of unconsciousness; mild convulsions may be associated with the syncopal attacks. A definite aura is usually present; this consists of weakness, lightheadedness, spots before the eyes, and epigastric distress. Patients often turn pale, perspire profusely, and complain of sensation

of numbness in the extremities. During the unconscious attacks the pupils usually dilate; during one of the induced attacks there was a definite exophthalmos which receded quickly at the termination of the attack. The vertigo usually comes on in the attacks, the patient being usually free from dizziness between the attacks. During the attacks of vertigo patients often stagger and occasionally fall. The attacks of unconsciousness usually last from a few seconds to fifteen or twenty minutes; the average attack lasts one to four minutes. The spontaneous attacks of unconsciousness practically always occur when the patient is either sitting or standing and rarely when the patient is lying down. Attacks of fainting occasionally are precipitated by changing the position of the body, turning the head to the right or left, or looking upward. Any pressure on the neck, such as tight collars or carrying sacks of grain on the shoulders, also may bring on attacks. It is common for spells to occur in barber chairs when towels are placed rather tightly around the patient's neck and when the patient changes the position of his body rather quickly. In most instances, the precipitating factors in the spontaneous attacks are unexplained.

BLOOD PRESSURE DURING THE ATTACKS

There has not been an adequate study of the blood pressure during spontaneous attacks. In the induced attacks the blood pressure usually decreases; this decrease varies from a slight to a severe depression of blood pressure. The fall in blood pressure was greatest in cases of hypertension. In a few instances there was a slight rise in blood pressure during the induced attacks.

In the attacks of unconsciousness the patient may have a mild or a severe convulsion. Patients practically never bite their tongues or lose control of their sphincters. The induced attacks are usually of shorter duration than the spontaneous ones. The diagnosis is made from the history and by inducing an identical attack by making graded pressure on one of the carotid sinuses. It should not be necessary to induce an attack by making pressure on both sinuses at the same time.

TECHNIC IN EXAMINING PATIENTS FOR HYPERSENSITIVE CAROTID SINUS

The patient should preferably be in a sitting position, with the head tipped slightly backward to one side and away from the side being examined. The sinus is usually situated just below the angle of the jaw and at the level of the upper border of the thyroid cartilage. The situation is somewhat variable, however. The carotid bulb frequently can be definitely palpated. Pressure is made with the thumb, compressing the sinus against the spinal column. The characteristic response will usually occur in ten to twenty-five seconds. This depends on the efficiency of the examiner and the sensitivity of the sinus.

TREATMENT

In a certain portion of the cases the symptoms are mild and the attacks occur so infrequently that no treatment is required. In cases in which the attacks are moderately severe, the patients are advised to avoid turning their heads quickly, looking upward and stooping suddenly; they also should avoid any constriction on the neck, especially tight collars.

The drugs that are usually recommended are ephedrine, epinephrine, benzedrine, and atropine. In my experience, drugs have not proved particularly satisfactory.

Operation is the treatment of choice in cases in which the attacks are moderately severe or severe. The operation consists of denervation of the carotid sinus and portions of the common, external, and internal carotid arteries.

Prognosis.—This is not a killing disease. I do not know of a proved case in which the patient died in an attack. As far as recovery is concerned, patients may have these attacks for many years.

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THE USE OF QUINIDINE SULFATE INTRAVENOUSLY IN VENTRICULAR TACHYCARDIA*

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PAROXYSMAL ventricular tachycardia occurs very infrequently and, with very few exceptions, appears in patients with serious structural heart disease. Its appearance is often an indication of an impending fatal termination. In these respects it differs entirely from paroxysmal auricular tachycardia which is of common occurrence, rarely appears in people with structural heart damage, and seldom turns the scale against the patient.

Of this series of 26 cases of ventricular tachycardia two are from the private records of Dr. J. A. Oille and the remaining 24 are from the wards of the Toronto General Hospital. These 24 cases occurred during the past seventeen years and show the rarity of ventricular tachycardia, as during that time electrocardiograms have been done on 12,000 patients having or suspected of having heart disease. Cardiac infarction was the diagnosis in 12 of the 26 cases, the infarction having occurred from a few hours to several weeks before the onset of ventricular tachycardia. Four were cases of degenerative heart disease. Two patients were suffering from hypertensive heart disease, one of them also having uremia. Chronic rheumatic heart disease accounted for three cases. Too liberal administration of digitalis may have been the cause of the ventricular tachycardia in three cases, as the tachycardia was preceded by frequent extrasystoles and cleared up on stopping the digitalis. However all three died a few days later. Ventricular tachycardia appeared in a case of chronic rheumatic heart disease and in a case of hyperthyroidism, both of which were being given quinidine sulfate by mouth in an attempt to clear up auricular fibrillation. We believe that the ventricular tachycardia in these two cases was due to quinidine sulfate administration.

Definite structural heart disease was present in all the cases except the hyperthyroid case, a man of thirty-five who was being given quinidine by mouth preoperatively for auricular fibrillation. We no longer use quinidine preoperatively in cases of hyperthyroidism for two reasons: normal rhythm is likely to reappear following opera-

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Read before the American Heart Association, section on cardiac disorders, at Atlantic City, N. J., June 8, 1937.

tion, and when auricular fibrillation has been stopped preoperatively by quinidine the fibrillation frequently reappears following operation.

We have included no cases in which the paroxysms of tachycardia were of brief duration. In several of these cases the paroxysms lasted for several days continuously. Only cases of longer duration are considered because of the impossibility of evaluating the results of any form of treatment in paroxysmal attacks of any kind, particularly if the paroxysms are of short duration.

While ventricular tachycardia can often be recognized clinically, the diagnosis was made or confirmed in all our cases electrocardiographically.

It is well recognized that digitalis, mecholyl, and carotid sinus stimulation have no effect on ventricular tachycardia. The attacks either end spontaneously or are stopped by quinidine sulfate. We have tried digitalis, mecholyl, and carotid sinus stimulation on several of the cases without any results.

The onset of ventricular tachycardia is often accompanied or followed by a profound degree of shock, as evidenced by marked fall in blood pressure, cyanosis, dyspnea, nausea, vomiting, and even coma. Nine of our patients were severely shocked, while the remainder appeared to be little if at all upset by the ventricular tachycardia. Seven of the 9 cases showing marked shock had had cardiac infarction recently or fairly recently. The diagnosis in the other two cases was hypertensive heart disease with uremia in one and degenerative heart disease in the other.

The fact that a marked degree of shock accompanied ventricular tachycardia in only 9 of the 26 cases naturally raises the question as to whether the shock was due to the ventricular tachycardia or to the underlying heart condition. The immediate and invariable improvement in the shocked patients on the restoration of sinus rhythm strongly suggests that in these cases at any rate the shock was due in part at least to the abnormal rhythm.

Prior to 1931, when we began to use quinidine sulfate intravenously in cases of ventricular tachycardia, all our cases showing this rhythm died within a few days of the onset of ventricular tachycardia, with the exception of the cases in which the ventricular tachycardia was due to quinidine given to clear up auricular fibrillation.

Quinidine sulfate was used intravenously only when shock was severe and vomiting made the oral administration of the drug impossible.

Administration.—Quinidine sulfate is relatively insoluble in water and we have found that it can be dissolved more readily in 5 per cent glucose or in normal saline solution. By vigorous shaking 50 to 60 grains can be dissolved in 500 c.c. of 5 per cent glucose. The solution is then filtered and given intravenously, slightly warmed, at the rate of 100 to 120 c.c. an hour. While it is being administered, blood pressure readings are taken frequently on the other arm.

We have given quinidine sulfate intravenously to 9 patients, one of them receiving a dose on three different admissions. One case, a man of thirty-six, was admitted two weeks after an attack of coronary thrombosis. On the day after admission he developed ventricular tachycardia and his blood pressure fell to 90/78. Carotid sinus stimulation was tried on both sides without effect. Intravenous quinidine sulfate was then started and after 9 grains had been given he complained of low sternal pain, became restless and more cyanosed, and his blood pressure fell to 70/?. Quinidine was discontinued and coramine given intravenously but the blood pressure continued to fall to 50/?. Fifteen grains of caffeine sodio-benzoate intravenously brought the blood pressure up to 104/76 in five minutes and his dyspnea, color, and pain improved. Next day, ventricular tachycardia still being present, digoxin and strophanthin were tried unsuccessfully and, vomiting being no longer present, he was given quinidine sulfate by mouth, 10 grains hourly for three doses. After an interval of three hours the same dose was repeated and on the following morning normal rhythm was present.

This is the only case in which quinidine sulfate intravenously seemed to have an adverse effect, but the subsequent progress of the patient has been satisfactory as he is well and at work two and a half years later.

A fairly typical case was H. N., a male aged thirty-five years, admitted July, 1935, with the following history. On the day before admission he had severe epigastric oppression with heart pounding and several syncopal attacks and vomiting. He was admitted to hospital deeply unconscious, with Cheyne-Stokes respirations and cyanosis and appeared to be moribund; blood pressure 60/0; heart rate 230. Electrocardiogram showed ventricular tachycardia. By the time intravenous quinidine sulfate was started his heart rate was 250; in twenty minutes his heart rate was 160 and blood pressure 94/60; in one hour the rate was 140 and blood pressure 100/70; in one hour and thirty-five minutes the rate was 72 and blood pressure 114/80. He received 17 grains of quinidine sulfate and was conscious and comfortable before the intravenous injection was discontinued. A few days later ventricular tachycardia reappeared, with a heart rate of 250, but without vomiting. He was given two doses of 15 grains of quinidine sulfate by mouth and during the ensuing three hours his heart rate fell: 250—200—160—80. Electrocardiograms showed changes typical of coronary thrombosis. After six weeks in bed and a few weeks convalescing he returned to his former work and was still well in June, 1937.

This case was exceptional in that the heart rate was much faster than in the others in which it usually ran from 160 to 180 per minute.

The average amount of quinidine administered to the patients in this series was slightly less than 20 grains. One patient received 35 grains.

Of the 9 patients treated intravenously since 1931 three are dead, one succumbing to another attack of coronary thrombosis two weeks after the ventricular tachycardia. Another had hypertensive heart disease and the ventricular tachycardia had been present for two days before quinidine was used. After 20 grains intravenously, ventricular tachycardia stopped but the patient died of uremia a week later. The third fatal case was that of a man who since 1931 had six admissions to the hospital for attacks of coronary thrombosis. On five of the admissions ventricular tachycardia was present. On three occasions he seemed moribund, was pulseless, and received quinidine sulfate intravenously. On two occasions the ventricular tachycardia was not accompanied by severe shock and quinidine sulfate was given by mouth. He died in December, 1935, and the autopsy showed extensive sclerosis of the coronary arteries, the left anterior descending branch being a double vessel with recanalized thrombi and recent thrombi, and old and recent infarcts of the apex of the left ventricle and adjoining septum. The remaining six patients are alive.

The fate of the 17 cases of ventricular tachycardia not receiving quinidine sulfate intravenously is of interest. Three are alive, the other 14 having died within fifteen days of the onset of ventricular tachycardia. Of the 3 who survived, two were the cases in which ventricular tachycardia was believed to be due to quinidine sulfate therapy for auricular fibrillation. The third was a case of coronary thrombosis. Ventricular tachycardia appeared twenty-six days after the coronary thrombosis and was accompanied by a slight fall in blood pressure. The ventricular tachycardia disappeared after one dose of quinidine sulfate by mouth.

SUMMARY

Ventricular tachycardia is at times accompanied by shock of such severe degree that the patient appears to be moribund. This state of shock is due, in part at least, to the ventricular tachycardia, as improvement is marked when normal rhythm is restored.

We recognize the difficulty of evaluating the treatment of any paroxysmal affection, but when six out of 9 cases treated intravenously are alive for periods up to four years, and only one of the remaining 17 cases lived longer than fifteen days (omitting the two cases due to quinidine administration), we feel that the administration of quinidine sulfate intravenously may be life-saving.

We suggest that the intravenous administration of quinidine sulfate be restricted to cases of ventricular tachycardia in which shock and vomiting preclude the oral administration of quinidine sulfate.

Department of Reviews and Abstracts

Selected Abstracts

Lendle, L.: The Factors Involved in the Action of K-Strophanthidin (Distribution, Elimination and Cumulation) and the Effectiveness of Several Strophanthidin-Ester Combinations. Arch. f. exper. Path. u. Pharmakol. **182**: 72, 1936.

Ester combinations of K-strophanthidin were as effective on the frog as the genin but only one-half to one-third as effective as the glucoside. Even the most active ester combination (isovaleryl ester) is less effective than K-strophanthin in warm-blooded animals. The lethal dose given of the genin subcutaneously is five times the doses used intravenously, whereas in the case of the glucoside, the subcutaneous lethal doses are only twice the intravenous. It was found that 12.3 per cent of the fatal dose of the glucoside is excreted per hour while 25 per cent of the fatal dose of the genin is excreted per hour. One-tenth of the total fatal dose of glucoside is bound by the heart, the genin is apparently bound in the same proportions.

The smallest cumulating dose of the genin is 15 to 20 per cent of the fatal dose whereas for the glucoside, it is 7 to 10 per cent.

These studies indicate that the difference between glucoside and genin is only a quantitative one.

L. N. K.

Dieckhoff, J.: Power of the Heart With and Without Hypertrophy With Aortic Insufficiency as Determined in the Heart-Lung Preparation. (The Action of Digitalis on Such Preparations.) Arch. f. exper. Path. u. Pharmakol. **182**: 268, 1936.

The production of aortic insufficiency in the cat heart causes a decreased duration as compared to the normal heart of the viability of the heart when used under strain in the heart-lung preparation. The power of the aortic insufficiency heart is decreased also. This effect is found during the first sixty days following aortic insufficiency. Hearts having this lesion for one hundred to one hundred and fifty-four days and showing marked hypertrophy approach the normal power in the heart-lung preparation. The use of an artificial valve to prevent an aortic leak restored the nonhypertrophied heart to normal power. In the hypertrophied heart the artificial valve makes the heart more efficient than normal. Preliminary digitalization of the heart with aortic insufficiency makes it more powerful.

L. N. K.

Straub, W., and Scholz, J.: Studies on the "Vagus Substance." Arch. f. exper. Path. u. Pharmakol. **182**: 331, 1936.

A new method of studying humeral transmission of vagus action is described. The inhibition of esterase by physostigmin and prostigmin is demonstrated. Hydrocyanic acid has a similar action. All three substances, therefore, enhance the effect.

L. N. K.

Friedrich, L. V.: Is Heart Action Influenced by the Gastro-Intestinal Tract? Arch. f. Verdauungskr. **60**: 67, 1936.

In cases of patients with either normal or diseased hearts, distention of the gastrointestinal tract with air or other gases has no influence on the heart rate or the blood pressure, except when the diaphragm is elevated. Under the latter circumstance, pain may occur.

L. N. K.

Zaeper, G.: Measurement of Pulmonary Blood Flow. Beitr. z. Klin. d. Tuberk. **88**: 79, 1936.

A method is presented for clinical use based on the Fick principle. Alveolar air and saturation of the blood are used in calculating the A-V O_2 difference. This and the O_2 consumption per minute is the basis of flow determination. Four trained individuals had a minute volume flow of 20.8 liters on the average. Five untrained individuals had a minute volume flow of 28.2 liters.

L. N. K.

Lucadou, W. v.: The Adrenals in Chronic Heart Involvement. Beitr. z. path. Anat. u. z. allg. Path. **96**: 561, 1936.

The medulla of the adrenal is hypertrophied in chronic cardiac patients whether renal or essential hypertension is present or not. In patients with chronic nephritis and hypertension, an increase is shown in the size of the adrenal cortex as compared to those without these complications.

L. N. K.

Pfuhl, W.: The Manner in Which Heart Action Is Assisted by Intrathoracic Suction. Deutsches Arch. f. klin. Med. **179**: 247, 1936.

The filling of the heart is aided by an elastic pull of the lungs. This is equivalent to a pull of 3 to 5 kilograms during normal breathing. It acts on the auricles during ventricular systole, on the ventricles during auricular systole and on the whole heart during diastole. Part of ventricular systole is used to augment this lung suction power.

L. N. K.

Gurewitsch, J. B.: Variability of Heart Size. An Investigation of 193 Pairs of Twins. Fortschr. a. d. Geb. d. Röntgenstrahlen **54**: 62, 1936.

The ages of the twins studied were from four to eleven years. It was found that size, weight, and chest diameter have an equal effect on heart size, but their effect is not great. Previous disease (one and one-half to two years before examination) such as scarlet, diphtheria, and typhus have no effect.

L. N. K.

Seekles, L.: Action of Magnesium on the Heart. Klin. Wchnschr. **15**: 1434, 1936.

Tachycardia, block, and standstill occur following the intravenous use of calcium chloride in veterinary fields. The use of magnesium chloride in the proper dose avoids the danger of block and standstill, the ratio being 4 parts of calcium to 1.5 of magnesium.

L. N. K.

Aschenbrenner, R.: The Digitalis Electrocardiogram. Klin. Wchnschr. **15**: 1039, 1936.

The depression of the S-T segment following digitalis is attributed to a slowing of ventricular conduction. Strophanthin as distinguished from other digitalis preparations does not change the S-T segment; this is thought to indicate a less marked effect on conduction by this drug.

L. N. K.

Schwingel, E.: Value of the Initial Complex of the Electrocardiogram as a Test of Heart Function. Ztschr. f. d. ges. exper. Med. **98**: 539, 1936.

In normal persons exercise causes a decrease in QRS duration. In patients with heart disease QRS duration is increased with exercise.

L. N. K.

de Châtel, A.: The Abnormal Deviations of the Final Complex of the Electrocardiogram in Local Leads, III. Ztschr. f. d. ges. exper. Med. **99**: 207, 1936.

The effect of cardiac dilatation on the T-wave was determined. The dilatation was produced in the dog by compression of the aorta or the pulmonary artery. Dilatation of the right ventricle makes the T negative and dilatation of the left ventricle makes the T taller. Local (unipolar) leads show that this is due to earlier deactivation of the dilated chamber.

L. N. K.

Schlomka, G., and Reindell, H.: Concerning the Clinical Electrocardiography. V. The Changes in the Curve With Shift From the Reclining Position to Standing. Ztschr. f. klin. Med. **130**: 313, 1936.

The authors found that not only does the pulse accelerate on standing up, but QRS becomes smaller and T becomes notched or diphasic. At times, the electrocardiogram may resemble that in coronary occlusion when the subject stands up. These are reversible changes, reaching a maximum in 8 to 15 seconds and usually receding after a few minutes. Despite acceleration of the heart, systole may not shorten in duration. Changes are due in part to a lack of blood supply to the heart, following redistribution of blood on standing up and in part to stimulation of pressor nerve receptors. The degree of change in the electrocardiogram is a function of the state of the heart and the electrocardiographic changes on standing up may be used as a functional test of the heart. Its importance in aviation is emphasized.

L. N. K.

Faleiro, A.: Electrocardiographic Diagnosis of Ventricular Hypertrophy. I. Left Ventricular Hypertrophy. Ztschr. f. klin. Med. **131**: 147, 1936.

The author determined the potential quotient (Groedel's method) from the ratio of the major upward deflection of QRS in a precordial lead over the left parasternal line and that in the precordial lead over the left midaxillary line at the level of the xyphoid. This ratio was never more than 2.3 in males and 2.6 in females with normal hearts (250 cases) or heart disease without hypertrophy (140 cases). In left ventricular hypertrophy 80 per cent of the (41) cases had values over 2.5 in males and 3.0 in females. Cases with right ventricular hypertrophy (10) had values less than 0.8. This method, according to the author, is thus of value in determining hypertrophy.

L. N. K.

Faleiro, A.: The Localization and Prognosis of Anterior Wall Infarction With the Aid of the Electrocardiogram. Ztschr. f. klin. Med. **130**: 808, 1936.

The author reports 50 cases of anterior wall infarction and 30 of posterior wall infarction. The precordial lead from the apex showed a mainly or entirely inverted initial deflection in 20 of the anterior infarcts and in all cases of posterior infarction. In the rest of the anterior infarcts the QRS was positive with or without an initial negative phase. In 12 of these an apical infarct was demonstrated postmortem. In 80 instances without infarction, the QRS was inverted except in 5 cases of right ventricular hypertrophy in which the QRS was upright. In 29 cases of apical infarct precordial leads from the fourth intercostal space to the left of sternum, 27 showed an absence of the initial phase of QRS; in the others it was small.

L. N. K.

Riseman, Joseph E. F., and Brown, Morton G.: Medicinal Treatment of Angina Pectoris. Arch. Int. Med. **60**: 100, 1937.

The use of fifteen different drugs in the treatment of twenty-six patients with angina pectoris was studied. Each drug was given several times a day for at least a week before its effect was evaluated. The efficacy of treatment was ascertained by the usual clinical methods and also by determining how much work, under standardized conditions, the patient could perform before pain developed. Control observations were made to differentiate between spontaneous remissions and improvement due to treatment.

The patient's estimation of therapeutic benefit indicated that all the drugs were approximately equal in value. Placebos were just as often beneficial as other medicaments.

The exercise tolerance test revealed that patients whose treatment consisted of lactose, sodium bicarbonate, potassium iodide, or tissue extract were unable to perform any more work than was possible without medication.

Glyceryl trinitrate given before work was undertaken prevented attacks and enabled many patients to do considerably more work. This prophylactic effect was often of relatively short duration, but attacks were prevented for as long as an hour in many cases. Such patients could be rendered completely free from attacks in daily life by taking glyceryl trinitrate at hourly intervals. For all practical purposes small doses ($\frac{1}{500}$ grain, or 0.1 mg.) were as valuable as larger doses and were attended by little discomfort.

One-half of the patients were benefited by either aminophylline or quinidine sulfate. Aminophylline had to be given in doses of 3 grains (0.2 gm.) to be effective.

Theophylline calcium salicylate, erythrol tetranitrate, and atropine sulfate were often of value; occasionally they benefited patients not helped by either aminophylline or quinidine sulfate. The doses of atropine necessary frequently caused discomfort because of side reactions.

Codeine sulfate and phenobarbital rarely enabled the patient to do more work before pain developed, but these sedatives appeared to be of aid as an adjunct in the treatment of the patient.

Sodium nitrite and small doses of dinitrophenol were only rarely of benefit. Other more effective drugs are available, and dinitrophenol, even in the small doses used, occasionally gave undesirable side reactions.

Digitalis was rarely of value and frequently caused a striking increase in anginal attacks.

AUTHOR.

Battro, A., and Braun Menendez, E.: Electrocardiographic Studies of Mitral Stenosis. Rev. argent. de cardiol. 4: 1, 1937.

Simultaneous records of venous pulse, heart sounds, and electrocardiogram in 15 cases of mitral stenosis allowed the following conclusions:

The diastolic murmur, in cases of sinus rhythm, is definitely reinforced, during the rapid ventricular inflow and during auricular systole; in cases of auricular fibrillation the second reinforcement (presystolic murmur) is lacking, and the diastolic is so brief that it may simulate a sound. If the heart action is rapid, it occupies the whole diastole, and gets so close to the first heart sound that it may be clinically taken as a presystolic murmur. In cases of sinus rhythm the presystolic murmur may be absent in the event of a prolonged diastole. In all cases its ''in-crescendo'' character is inconstant.

The first heart sound often shows murmuric vibrations during the isometric contraction phase. They may be interpreted as a slight degree of mitral insufficiency. In cases with auricular fibrillation, especially after prolonged diastolic pauses, the first heart sound begins with a slow wave which practically coincides with the initiation of the QRS complex.

A three-sound rhythm frequently results from reduplicated second sounds or opening snap of the mitral valve. The former is more easily recognized at the base, whereas the latter is more easily found over the noncovered and apex regions, although they may be recorded from other areas and even simultaneously coexist. For the correct interpretation of the phonocardiograms the venous pulse record is necessary to furnish adequate reference points.

Even though a reduplication of the second sound was not systematically sought for, it was recorded in 5 cases. The opening snap was found in 7; in two of them it was clearly separated from the diastolic murmur by a short interval and in the remaining 5 the vibrations of the murmur immediately followed it, the snap being only recognizable by the higher amplitude and lower frequency of its vibrations. In the 8 remaining cases the beginning of the diastolic murmur coincided with the top of the wave of the venous pulse without any clear difference between the initial and consecutive vibrations.

AUTHOR.

Wilson, May G., and Schweitzer, Morton D.: Rheumatic Fever as a Familial Disease. Environment, Communicability, and Heredity in Their Relation to the Observed Familial Incidence of the Disease. J. Clin. Investigation 16: 555, 1937.

There is presented a consideration of the rôle of environment, contagion, and heredity as factors responsible for the familial incidence of rheumatic fever in 112 families, observed over a period ranging from three to eighteen years.

There did not appear to be a direct relation between the environments studied and the incidence of rheumatic fever. One-third of the 112 families lived under relatively favorable environmental conditions. In the former group the incidence of rheumatic siblings was 53 per cent, as compared with 46 per cent in the latter group.

There was no direct relation between the type and source of exposure and the resulting activity. The incidence of rheumatic fever following ''active exposure,'' and ''inactive exposure'' was comparable. Intimate contact (''familial exposure'') and casual contact (''extra-familial exposure'') were equally effective.

Only 21 per cent of 968 person years of active exposure could be related to subsequent rheumatic activity.

In a total of 55 families with rheumatic parents, in 47 per cent, activity followed active exposure; in 53 per cent, activity followed inactive exposure.

In 57 families with nonrheumatic parents, in 57 per cent, activity followed extrafamilial exposure (casual contact); in 43 per cent, activity followed familial exposure (intimate contact).

The interval between active or inactive exposure and the onset of rheumatism was one year in 20 per cent; two to five years in 49 per cent; and six to eleven years in 31 per cent.

The 227 rheumatic siblings experienced 588 calendar years of rheumatic activity. Of these years, 159, or 27 per cent, were simultaneous years of rheumatic activity.

The interval between the related manifestations was: One month, 29 per cent; one to two months, 24 per cent; two to eleven months, 47 per cent. Three-fourths of the related manifestations of rheumatic activity were between joint pains and other rheumatic manifestations. One-fourth of the related manifestations was between polyarthritis, carditis, and chorea. In 66 per cent the interval between these major manifestations was two to eleven months.

In 51 families, 59 parents (mother or father) were rheumatic; 44 per cent experienced rheumatic activity during the lifetime of the siblings. In no instance did a negative parent acquire the disease. The incidence of rheumatic siblings was comparable in families with a rheumatic mother or father.

Of 112 rheumatic families, 49 per cent had parental rheumatism. In only 28 per cent of the families were parents and pedigree on maternal and paternal sides apparently negative.

Of a total of 468 siblings over the age of three years, 48 per cent were rheumatic; 46 per cent males and 54 per cent females.

All identical twins cited (4 pairs) were alike in having rheumatic fever. Of the 12 pairs of fraternal twins, 5 pairs had similar incidence, i.e., both positive or both negative, and 7 pairs had dissimilar incidence.

A genetic analysis of the data corrected for size of family gave agreement between observed and expected values.

For children of 58 pairs of negative parents, the observed incidence was 94, the expected value 88.

For children of 37 positive mothers, the observed incidence was 90, the expected value 86.

For children of 29 positive fathers, the observed and expected incidences were respectively 29 and 27.9.

The hereditary mechanism involved was a single autosomal recessive gene. Dominance, involving one or more genes, and recessives involving two or more genes, as well as sex linkage were all excluded.

AUTHOR.

Palmer, J. H.: The Blood Pressure in the Years Following Recovery From Coronary Thrombosis. Lancet 1: 741, 1937.

An analysis was made of the blood pressure findings in 212 patients who survived an attack of coronary thrombosis by at least three months. The incidence of hypertension (160 mm. systolic and/or 100 mm. diastolic) as determined by readings made before or at any time after the attack, was found to be 73 per cent. More than half the cases showed hypertension during the first year. The hypertensive group included 37 per cent of those aged under fifty, and 78 to 84 per cent of those in the next three decades of life at the time of the attack. All except one of the 20 female patients were hypertensives.

The average course of the blood pressure during ten years after coronary thrombosis (not including the first month following the attack) has been plotted. The systolic pressure showed a slight rise during this period while the diastolic showed a slight fall.

Evidence is adduced to show that the average blood pressure for the series before the attack was probably about 170/100. Although on the average the prior levels were not regained during the ten-year period, they were in a few cases actually exceeded.

AUTHOR.

Kalbfleisch, H.: Phrenico-Pleural Collateral Circulation. Frankfurt. Ztschr. f. Path. **49**: 10, 1936.

A case of embolic-thrombotic closure of the left lower pulmonary artery in a fifty-two-year-old cardiac patient is described in which the blood supply came from collaterals from the diaphragm to which the lung had become adherent. The left bronchial artery was also found to be dilated.

A second case of Laennec cirrhosis of the liver, liver carcinoma, congestion of the systemic and pulmonary circuits in a fifty-five-year-old man is reported in which venous collaterals had been established between the portal vein, veins in the abdominal wall, and veins in the right side of the diaphragm. In addition venous collaterals were present betwen the diaphragm and the pulmonary veins of the adherent lung.

L. N. K.

Linton, Robert K.: Acute Peripheral Arterial Occlusion and Its Treatment. New England J. Med. **216**: 871, 1937.

In general, there are four types of treatment of embolism: (1) Embolectomy, (2) the use of intermittent negative and positive pressure, (3) the use of vasodilators, and (4) symptomatic or "watchful waiting." Embolectomy was successful in 4 out of 9 cases. Careful localization was made preoperatively, by means of palpation and the use of an aneroid sphygmomanometer. Negative-positive and negative pressure treatment was successful in 9 out of 12 cases. This is especially encouraging in that these cases were not suitable for embolectomy because of the poor condition of the patients. The average length of treatment necessary to establish an adequate circulation was four and one-half days. One of the patients treated successfully by means of negative-positive pressure had a large embolus occluding the bifurcation of the aorta and the arteries below the bifurcation. The author believes that early application of intermittent negative-positive pressures prevented formation of secondary thrombi in the arteries distal to the occlusion. The author has no data on the use of vasodilators, since he did not wish to complicate the results of the other methods of treatment. In only one of 13 cases receiving no treatment was the limb saved. Of 5 cases of embolus in the arm, 4 recovered with no treatment but these cases were not included because of the frequency of spontaneous development of collateral circulation in this extremity.

The best results from a single method of treatment of embolus was suction and pressure therapy. The writer believes the ideal method of treatment for suitable cases is a combination of treatments, namely, embolectomy followed by use of the suction-pressure treatment and also the production of peripheral vasodilatation. In cases properly treated, a still higher percentage of extremities should be saved.

H. M.

Pick, E. P.: Automatic Adjustment and Regulation of the Circulation. Presented at the International Medical Week in Lucerne, Sept. 1, 1936. Taken from an abstract in the Ztschr. f. Kreislaufforsch. **29**: 226, 1937.

In addition to nervous and neurohumoral regulation of cardiac activity, there is an important group of physical regulatory mechanisms; viz., diastolic, filling and distention of the heart, venous return, coronary flow, and pericardial restraint. The action of blood reservoirs in regulating blood volume and avoiding congestion is established, the liver being important in this connection. A number of metabolic products such as CO_2, lactic acid, histamine, and acetylcholine, adenylphosphoric acid are important in regulating the circulation. These and the hormones and vitamines form a second important mechanism. They operate not only directly on the circulating system but reflexly. A third mechanism is the blood pressure regulators, the end organs which tend to keep the blood pressure constant. These various stimuli summate (or neutralize each other) so that the circulation is well adjusted to its requirements.

L. N. K.

Heier, H.: Changes in the Wall of the Heart in the Roentgenkymogram. Fortschr. a. d. Geb. d. Röntgenstrahlen **53**: 895, 1936.

In one case diagnosis of aneurysm at the apex of the heart due to infarction was diagnosed with certainty only by the kymograph. It is valuable also in other types of myocardial damage and in pericardial adhesions. Changes in the amplitude of pulsations indicate myocardial disease; persistence of pulsations with a change in heart contour indicate extracardiac processes.

L. N. K.

Brenner, F., and Wachner, G.: Unusual Location of Cardiac Aneurysm and Its X-ray Diagnosis. Fortschr. a. d. Geb. d. Röntgenstrahlen **54**: 243, 1936.

A calcified bulge of the heart in the region of left pulmonary hilus was noted in the roentgenogram in a sixty-four-year-old subject. At autopsy this proved to be an old aneurysm of the posterior wall of the base of the left ventricle. It was associated with closure of the coronary ostia.

L. N. K.

Kalter, S.: The Glycocoll Metabolism in Degenerative Dystrophic Heart Disease. Deutsche Med. Wchnschr. **62**: 1371, 1936.

In a series of cases of myodegeneratio cordis, 5 grams of glycocoll was given 3 times daily. This caused improvement of the heart function in most cases.

L. N. K.

d. Gara, P.: Clinical Observations in the Treatment of Heart Disease With Gratusbaina and With Gratusbainose. Med. Welt. **10**: 1296, 1936.

They have a diuretic action. It is claimed that they make the pulse regular, raise low blood pressure, and lower high blood pressure (?).

L. N. K.

Beer, A. G.: Indication and Action of Scillaglucoside. München. med. Wchnschr. **83**: 929, 1936.

This presentation is based on a study of 123 cardiac patients. The cardiac action of this glucoside is less than that of strophanthin but its action in sup-

pressing the ectopic pacemakers is greater. It is quickly absorbed and quickly destroyed on oral or rectal administration as compared with other digitalis preparations.

L. N. K.

Donath, F.: Therapy of Acute Coronary Closure. Wien. klin. Wchnschr. 49: 692, 1936.

The author uses morphine together with caffeine and atropine as soon as the diagnosis is made. Morphine is repeated if necessary, and other narcotics such as pernocton are used. The author treats the stage with a drop in blood pressure with camphor, caffeine, strychnine, cardiazol, or coramin. During the healing stage, the patient requires six weeks' bed rest. No medication is necessary but euphylline may be used. Luminal to ensure sleep should be employed if necessary.

L. N. K.

PROCEEDINGS OF THE GERMAN SOCIETY FOR THE STUDY OF CIRCULATION

TENTH SESSION, BAD NAUHEIM, MARCH 13 AND 14, 1937*

1. **Vasodepressor Substances. H. Dale** (London).

While a number of vasodilator substances derived from tissue extracts are known, there is no direct evidence of their playing any rôle in physiological regulation of vessel tone. Histamine is the first substance isolated and has recently been shown to act by stimulating the sensory nerve endings. Acetylcholine works directly on the cholinergic efferent nerve endings. Since histamine is so powerful, it must exist in the body in a bound form. The histamine in plasma comes from the body cells. The acetylcholine found in the blood plays little or no rôle normally. The increase in flow of blood during activity must depend on liberation of vasodilators in the contracting muscle. Knowledge concerning adenylic acid derivatives is still fragmentary and the same is true of other dilators since it is difficult to free them from histamine.

2. **Adrenalin and Adrenalin-like Substances. H. Rein** (Göttingen).

The confusion regarding adrenalin is due to the fact that it has been used too often in pharmacological rather than physiological doses. Adrenalin has a vasoconstrictor action and also increases the blood volume. Its significance is doubted as a normal regulator of the circulation. It is found that painful stimuli do lead to liberation of adrenalin, but whether this is of significance is yet unknown. It is possible that adrenalin in physiological doses acts to redistribute blood in the body. This is true in the case of exercise where the distribution between active and inactive muscle may be aided by adrenalin. Physiological doses of adrenalin cause an emptying of the blood reservoirs. In the heart-lung preparation, no effect could be demonstrated on the metabolism when physiological doses of adrenalin were used. Thus, adrenalin in physiological doses is not a circulatory stimulator but a circulatory regulator to make the distribution of blood more economical. In this, its action summates with nerve stimulation and with that of local metabolic products.

Fleisch (Lausanne) in commenting on these reports, pointed out that acetylcholine in the blood comes from active muscles. It appears whenever the blood pressure drops and at the death of the animal. It is thus a pathological sign.

*Abstracted from report by H. Bruner in Ztschr. f. Kreislaufforsch. 29: 320, 1937.

3. **Cystamin, a New Histamine-Like Blood Pressure Depressor Substance. H. Robbers** (Mannheim).

This is decarboxylated cystin. It causes a drop in blood pressure and acts on peripheral vessels. Subcutaneously, it causes a long lasting effect.

4. **Coronary Insufficiency Following Histamine Collapse and Orthostatic Collapse. H. Meessen** (Freiburg i. Br.).

Intravenous injections of histamine in large doses caused electrocardiographic changes in the rabbit such as are seen in coronary insufficiency. This is true also in orthostatic collapse. At necropsy, in the latter condition, disseminated myocardial necrosis appears twenty hours later. The redistribution of blood occurring in these two conditions leads to anoxia of the heart.

5. **Adrenals and Angina Pectoris. W. Raab** (Vienna).

It was found that anginal attacks can be precipitated in young healthy individuals by injections of adrenalin.

6. **Circulatory Disturbances and the Function of the Adrenal Cortex. S. Thaddea** (Berlin).

In cats the removal of the adrenals leads to bradycardia and a blood pressure drop which is relieved by adrenal cortex. In the heart-lung preparation of the dog, the cortical hormone decreases coronary flow. Electrocardiographic changes following extirpation of the adrenals; viz., S-T depression and T-wave inversion, tend to disappear after cortical hormone administration. Similar results are obtained in Addison's disease.

7. **Paraganglia in the Sympathetic System and in Cranial Nerves. M. Watzka** (Prague).

Three groups of paraganglia are found: chromaffine, nonchromaffine, and mixed. The chromaffine ganglia are sympathetic in origin. The others are of mixed nerve origin. All are rich in nerve fibers.

8. **Action of Strophanthin on the Circulation of Normal Persons. K. Gotsch** (Prague).

It is found that stroke and minute volume of the heart decreases when this drug is used on normal persons. By direct intraarterial injection and comparison with the control limb, it could be demonstrated that strophanthin increases O_2 consumption in the periphery.

P. Martini (Bonn) found an increase in stroke and minute volume flow with this drug.

9. **Pharmacology of Coronary Insufficiency. C. Kroetz** (Altona).

He believes that a combination of drugs is indicated for daily use; viz., quinidine, luminal, and nitrite by injection. This combination is especially valuable in severe status angiosus and in cardiac asthma. He advocates vitamin B_1 in myocardial infarcts and also points out the value of a pure preparation of glutathione which acts as a cardiac stimulant and coronary dilator.

A. Weber (Bad Nauheim) noted the fact that coronary insufficiency sometimes is clinically and electrocardiographically silent.

Heubner (Berlin) was opposed to the use of combinations of drugs.

10. **Heart and Circulation in Emphysema and Bronchial Asthma. A. J. Anthony** (Grissen).

No evidence of heart damage was noted clinically or in the electrocardiogram. At autopsy the heart showed disseminated degenerative changes which extended to the endocardium and caused mural thrombi. The histological changes resemble those seen in rabbits following caffein and adrenalin. Suspicion is aroused that in man the common use of the drugs is the cause of these changes.

E. Kirch (Erlangen) pointed out that hypertrophy of the right heart can be demonstrated postmortem in emphysema.

11. **The State of Circulation and Breathing of Man at Low Pressures. K. Matthes** (Leipzig).

An increase was noted in minute volume flow in the decompression chamber when the atmospheric pressure was lowered. No change occurred in circulation time from the lung to the extremities, hence th eincreased blood flow must be confined to the visceral organs.

12. **Effect of Anoxemia on the Venous Pressure of Healthy Individuals. G. Budelmann, A. J. Anthony, and W. Schwarz** (Hamburg).

Arterial anoxemia in reclining persons whether produced in decompression chamber or by breathing air with reduced O_2 content, causes a rise of venous pressure up to 5 cm. H_2O. The authors do not attribute this to heart failure but to a reflex action on the peripheral circulation. When collapse occurs and arterial pressure falls, venous pressure rises further.

13. **The Blood Flow in the Veins Near the Heart. E. Holzlöhner** (Kiel).

A new electrical tachograph was used for blood flow recording and a tachyogram of venous flow was obtained. A systolic acceleration in flow toward the heart was noted.

W. Böhme (Rostock) reported a confirmation of Holzlöhner's observations on venous flow in man based on his roentgenokymographic studies of movement of the heart base when the mitral valve was calcified. In animals he obtained similar data by injecting x-ray opaque materials in the circulation and making roentgenokymographs. He noted the marked movement of the A-V floor. In man iodöl drops were injected into the veins and a systolic acceleration in their movement was noted.

14. **Effect of the Carotid Sinus Reflex on Circulation, Respiration, and Metabolism. E. Koch, and H. Brüner** (Bad Nauheim).

Long continued stimulation of pressor receptors of the carotid sinus causes alteration of breathing and decreases the metabolism of animals.

15. **Hypophysis and Circulation. F. Schellong** (Heidelberg).

This is an interesting theoretical discourse. The posterior lobe of the pituitary liberates vasopressin and causes a "pale" hypertension, but the part played in this by central reflex action and kidney damage is not clear. A decrease in vasopressin causes a loss of capillary tone and a drop in diastolic pressure. Functional disorders of the basophyllic cells of the pituitary can cause a drop in diastolic pressure such as is seen in Basedow's disease. No evidence is present of a regulatory rôle for vasopressin. In pituitary hypotonia, it is the anterior lobe which is affected. He be-

lieves that the hypotonia of hypopituitary origin (anterior lobe) acts via the adrenals. In this condition there is found an inability to adjust the blood pressure to stresses such as standing and exertion.

Cushing's syndrome is discussed, and it is suggested that the adenoma may cause an increase in vasopressin, it may act on the hypothalamic centers, or may cause an increase in the corticotropic hormone and this in turn stimulates the adrenal cortex.

The rôle of the pituitary in essential hypertension is discussed, and it is concluded that it is not primarily concerned, although it may play a subsidiary rôle in determining the constitutional disturbances which lead to the condition. The rôle of the basophilic cell hypertrophy in this condition is not settled.

16. **Hormones and Circulation in Gynecology. W. Haupt** (Jena).

Sex hormones play an important rôle in women, viz., in the menstrual cycle and menopause. Hormones are also important during pregnancy. In addition there is a great change in the circulation in pregnancy due to the need of supplying blood to the placenta. In eclampsia an increase can be demonstrated in vasopressor and antidiuretic substances of pituitary origin. They may be responsible for the symptoms, but this has not been established.

17. **Circulation in Disturbances of Blood Sugar Regulation. M. Bürger** (Bonn).

Small doses of hypertonic sugar appear to relieve spastic states perhaps by liberating a vasodepressor substance from the tissues. In tumors of the adrenals, hypertension, hyperglycemia, and glycosuria occur which disappear when the tumor is removed. Hypoglycemia has been reported in Addison's disease. The pancreas produces a sugar regulating hormone, insulin, and extracts from it give substances on the acting circulation, vagotonin and kallikrein. In young diabetics there is a hypotension. Hypertension occurs in elderly diabetics, and many of these are insulin resistant. The author believes that the latter state is due to a slowed circulation. In hypoglycemic shock the blood pressure drop is due to peripheral dilatation (chiefly in the capillaries). It is important to differentiate this state from diabetic coma. In lesser degrees hypoglycemic shock causes tachycardia, palpitation, headache, and irritability.

18. **Circulation in Thyroid Disturbances. G. W. Parade** (Breslau).

The thyroid operates through its regulation of the body metabolism. It acts also over the sympathetic nervous system. In myxedema there is a slowed circulation, a small pulse pressure, a decreased tone of the heart, and a flattening of the P- and T-waves in the electrocardiogram. In hyperthyroidism, the minute volume flow is increased, partly reflexly and partly by the local increase in metabolism. Sinus tachycardia is due to an adjustment of the nervous balance.

19. **Effect of Puberty on the Blood Pressure. P. Schenk** (Danzig).

He points out the hormones play a rôle in this period.

20. **So-called Pigment of the Heart Muscle and Skeletal Muscles and Its Relation to Muscle Function. R. Bohmig** (Rostock).

Microscopic investigation of the distribution and quantity of lipofuscins in human and ox hearts and in their skeletal muscles is reported. In the atropic muscle a decrease is shown in the quantity of this pigment. In the heart there is more of this pigment beneath the endocardium than beneath the epicardium. This is the reverse of vitamine C distribution.

21. **Determination of the Surgical Approach to Peripheral Vascular Disease. H. W. Passler** (Heidelberg).

Acetylcholine is used to determine the functional and organic components in peripheral vascular disease, in order to predict the value of sympathectomy in the case.

22. **Electrocardiographic and Kymographic Studies on Athletes After Exertion. H. Reindell** (Freiburg).

A prolongation of A-V conduction time was found in most athletes. Also, a prolongation of systole was noted. The roentgenkymogram shows characteristic changes. Following exercise systole is shortened.

Frey (Bern) pointed out that sports lead to right ventricular dilatation.

Staehelin (Basel) pointed out that depression of the diaphragm in athletes can alter the electrocardiogram and x-ray film.

23. **Calculations on the Basis of the Probability Theory of Parasystole in Auricular Fibrillation. S. Koller** (Bad Nauheim).

This presentation is theoretical.

24. **A Tension Electrocardiograph for Quantitative Work for the Practitioner. K. Gross** (Erlangen).

25. **Unipolar Leads of the Electrocardiogram. R. Schwab** (Würzburg).

Two points with maximum potential can be found on the chest, but these are not indications of the right and left ventricle respectively. In unipolar leads from the anterior surface of the heart in animals, all initial complexes show a general similarity, and there is no difference between the two ventricles.

E. Koch (Bad Nauheim) suggested the use of the entire body surface as the indifferent electrode.

L. N. K.

PROCEEDINGS OF THE GERMAN SOCIETY OF INTERNAL MEDICINE FORTY-NINTH SESSION, WIESBADEN

MARCH 15 TO 18, 1937*

1. **Action of Digitalis on the Central Nervous System. Marx** (Berlin).

This central action is indicated by (a) the improvement noted clinically when the blood flow is normal, (b) its stimulating (caffein-like action) in shock, (c) the antipyretic action of digitalis; this occurs also in noncardiacs. Injections of small doses of strophanthin into the ventricle of the brain of the dog causes sinus tachycardia, ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation and death. Evipan injections tend to prevent these effects. The action of digitalis injected into the cerebral ventricles is 10 or 100 times more powerful than when used intravenously. Sectioning the vagi does not always abolish this action of digitalis so that the sympathetic nerves as well as the vagi serve as efferent paths.

*Abstracted from a report by K. Seggel in Ztschr. f. Kreislaufforsch. 29: 335, 1937.

2. **Experimental Studies of Coronary Dilator Substances. Frey and Hess** (Freiburg).

A Rein stromuhr was used to measure flow in the right coronary artery at the same time that arterial blood pressure was determined in dogs anesthetized with morphine and pernocton. Sugar, papavydrin, novophyllin, cardiotrat, and deriphyllin cause an increased coronary flow and a drop in blood pressure, hence their action is dilator. The latter two have the longest action and are useful clinically.

3. **Clinical Studies on the Partial-Electrocardiogram in Man. Ernst** (Tübingen).

This is a procedure introduced by F. Groedel for obtaining precordial leads. It permits, in the author's opinion, localization of lesions to one or another ventricle. (This is not convincing.) Sometimes it shows electrocardiographic changes when none are present in the limb leads.

4. **The Stimulating Substance in Hypertension, Its Properties and Action. Westphal and Sievert** (Hannover).

It was found that the ultrafiltrate of the blood of 150 patients with hypertension has a pressor action in cats, rabbits, dogs, and humans. Its action is peripheral; it resembles the pressor substance obtained from the posterior lobe of the pituitary. When 2 c.c. of ultrafiltrate was given daily to rabbits, a protracted hypertension, a hypertrophy of the adrenals, and an increase of its cholesterin content was observed in these animals. The rise in blood pressure in rabbits is 50 mm. Hg in essential hypertension and little in the renal form. The rise in the rabbit is proportional to the pressure level in man. In preparing the ultrafiltrate, one must make the blood acid, pH 4, as it is unstable in alkali. It is also unstable in the presence of ultraviolet light. It is adsorbable on talcum, and a second injection is less effective than the first. It is not adrenalin, and it is not the substance isolated by Bohn. It acts in the decerebrated cat, it decreases flow in the perfused rabbit's ear, and it constricts the rabbit's coronary artery.

In the discussion, *Volhard* (Frankfort) supported this work, but *Marx* (Berlin), *Jores* (Hamburg), and *Raab* (Vienna) questioned it.

L. N. K.

Book Reviews

DISEASES OF THE HEART. By Sir Thomas Lewis. 2nd Edition. 295 pages with 45 illustrations. New York, 1937. The Macmillan Company.

In the preface to the first edition Sir Thomas Lewis wrote: "The impulse to write a book of reference has not stirred me, but I have had the desire to place at the disposal of students and medical practitioners the outline of my clinical teaching on diseases of the heart, as this has developed in my talks to my own hospital students. In beginning that teaching twenty and more years ago, I determined that the basis of what I taught should be that which I myself had seen and proved to be true. A second ideal that I have striven hard to attain is simplicity in teaching." This book is more than an outline; it is a study of diseases of the heart in which essentials are emphasized and nonessentials are carefully omitted. Such a book can be written only by one who is a master, and such a book is far more valuable than many volumes of greater length.

The appearance of the second edition is welcomed, not because there are many changes and additions, but because there are few.

Because of the logical arrangement of material and the simple clarity of style this work should be on the required-reading list for all medical writers.

THE DEVELOPMENT OF CARDIAC ENLARGEMENT IN DISEASE OF THE HEART: A RADIOLOGICAL STUDY. By J. H. Palmer, M.D. Special Report No. 222 issued by the Medical Research Council. London, 1937, His Majesty's Stationary Office. Price 1s. 0d. net.

This monograph of some fifty pages presents the results of a radiological study of the progressive changes in the size of hearts, and of their several chambers, the seat of organic disease, and the correlation of these changes with the clinical aspects of the disease. The object in view has been "to study the dynamic process of enlargement in various diseases rather than the static condition of the heart seen at any one stage."

The work was carried on in the cardiac department of the London Hospital under the direction of Dr. John Parkinson.

While the report does not claim to be comprehensive and complete it seems to enlarge the field of usefulness of radiological study in connection with diseases of the heart and gives interesting facts covering the progressive changes in the heart's size in such conditions as persistently increased heart rate, high blood pressure, congestive failure, and coronary thrombosis.

LES MÉTHODES CHIRURGICALES DU TRAITEMENT DE L'ANGINE DE POITRINE: ÉVOLUTION ET RÉSULTATS. By Marcel Bérard (with a preface by Professor René Leriche) 389 pages, Paris, 1937, Masson & Cie.

Dr. Bérard believes that there is a definite place for surgery in the treatment of angina pectoris and that operation should be considered in any case which is resistant to other forms of therapy, except, of course, when there is evidence of cardiac insufficiency. In this volume he discusses the reasons for and results of the various operations that have been suggested or performed for the relief of angina pectoris. After reviewing the anatomy and physiology of the nerves of the heart

and the nature of the anginal attack, he takes up the different operations, which he lists as those having an anatomical basis (that is, those operations that seek to interrupt the pain pathways) and those with a physiological basis (those which aim to interrupt the reflexes initiating an attack or to establish coronary vasodilatation). Of the various procedures he favors stellectomy as performed by Drs. Leriche and Fontaine. He also discusses the possibility of revascularization, citing Beck's work in Cleveland, and total thyroidectomy. He gives brief case reports of thirty cases of total thyroidectomy from the Peter Bent Brigham Hospital and comes to the very definite conclusion that the results of this form of treatment are unsatisfactory.

Dr. Bérard has provided an interesting summary of what has been done or attempted surgically for the relief of angina pectoris. As a summary the book could be greatly condensed with advantage. While angina pectoris is very common, the surgical treatment is relatively unusual, and in spite of this volume and a long bibliography, the final word on the subject has not been spoken.

LES ENDOCARDITES MALIGNES PROLONGÉES. ETUDE ANATOMO-CLINIQUE ET EXPERIMENTALE. By André X. Jouve. 354 pages with 50 illustrations, Paris, 1936, Masson & Cie, price, 50 fr.

The author provides a detailed bacteriological and anatomical study of bacterial endocarditis, considering the lesions of arteries and of other organs as well as those of the heart. He has succeeded in producing the disease in dogs and believes that the experimental findings add to an understanding of the disease in man. The lesions are illustrated by means of photographs and microphotographs, and there is an extensive bibliography.

L'EMBOLIE PULMONAIRE. RECHERCHES CLINIQUES, ANATOMIQUES, PATHOGÉNIQUES ET THÉRAPEUTIQUES SUR LES EMBOLIES ET LES INFARCTUS DU POUMON. By Pierre Bardin. 192 pages with 11 figures and 2 colored plates. Paris, 1937, Masson & Cie, price, 35 fr.

The thesis of this volume is the importance of nervous reflexes in cases of pulmonary embolism. Dr. Bardin notes that sudden death after pulmonary embolism does not bear a definite relation to the size of the vessel occluded and that thoracic surgeons can tie off a large pulmonary vessel without producing sudden death. He believes that when sudden death occurs it is the result of a reflex arising from the effect of embolic material on the nerve endings of the pulmonary *arterioles* and that a nervous predisposition, a hypervagotonia, is an important factor in this reflex. He believes that with arterial obstruction anywhere in the body the excitation of nerves in the vessel wall is far more important than obstruction to the flow of blood.

Dr. Bardin reviews the experimental work of others and his own work. In dogs he found it practically impossible to produce sudden death from a large pulmonary embolus and he has studied in detail the effect of various procedures designed to alter the neurovegetative or humoral conditions and so to study the reflexes arising from pulmonary embolism under different experimental conditions.

The author also discusses treatment and gives an extensive bibliography. While interesting from an experimental point of view, the book has many weaknesses on the clinical side.

LA DÉRIVATION AURICULAIRE S5 ET LA TRÉMULATION AURICULAIRE. By B. Pinchenzon. Preface by Professor C. Lian. 80 pages. Paris, 1937, J.-B. Baillière et Fils.

Stimulated by his master, Professor Lian, Pinchenzon has written a short book dealing with two subjects; first, the value of a certain electrocardiographic chest lead (called S5), with one electrode over the manubrium sterni and the other at the

inner end of the fifth right intercostal space, in revealing the electrical activity of the auricles when obscurely shown in the classical leads, and second, the clinical analysis of the intermediate stage of the auricular circus movement between auricular fibrillation and auricular flutter, variously labelled in the past as flutter-fibrillation or impure flutter or coarse fibrillation, but which Pinchenzon and Lian would like to establish as a definite electrocardiographic and clinical entity called "auricular tremulation."

The author appends 20 brief case reports and publishes two records showing "auricular tremulation" and one showing "fibrillo-tremulation."

Doctors Pinchenzon and Lian have done us a service in calling attention again to the value of certain chest leads in studying auricular action when the classical leads fail to define it. The very first human electrocardiogram ever published was from a chest lead in the days before the more convenient limb leads were arbitrarily selected. Then later on Lewis and others reintroduced chest leads for the study of auricular activity, but these did not assume any important place in clinical electrocardiography, largely because of the apparent rarity of their need. In this country, the recent introduction of chest leads in routine electrocardiography for the detection of ventricular myocardial disease has proved so important and valuable that the less important chest lead points, such as Lian and Pinchenzon's Lead S5, for the study of the auricles have been overlooked. It may well be that on certain occasions they should be employed, not only this particular lead labelled S5 but others perhaps at various angles to it; other features of auricular activity not clearly shown by Lead S5 might thereby be revealed.

"Auricular tremulation" as a designation for the stage of the auricular circus movement intermediate between auricular flutter and auricular fibrillation does not seem advisable as yet for routine use until further work and experience have proved its value. It may well turn out to be a more satisfactory term than flutter-fibrillation if it can cover the range of circus movements between flutter and fibrillation, but it seems likely that there are still border lines which would have to be designated "tremulation-flutter" or "tremulation-fibrillation." Rather than to introduce a new term for such, why not use as needed the terms we already have, in gradation as follows: flutter, impure flutter, fibrillation-flutter, flutter-fibrillation, coarse fibrillation, and fibrillation. However, the utility and wisdom of such subdivision are frankly open to question. To the reviewer the term flutter-fibrillation is still adequate to cover the range of auricular arrhythmia between flutter and fibrillation. He and most others have employed the term to signify this intermediate mechanism, labelled in this book auricular tremulation, and not to signify alternate periods of auricular fibrillation and auricular flutter which should be designated by point of time, not as a joint arrhythmia.

Fortunately, clinically it is of little importance apparently to identify this particular phase of auricular arrhythmia—tremulation—by a chest lead, for etiologically, prognostically, and therapeutically it appears to have the same significance as auricular fibrillation and auricular flutter and should so be treated, as it doubtless is being treated most of the world over.

However, the skepticism of the reviewer should not by any means be considered as a bar to the further study of auricular action by chest leads or to the analysis of this auricular mechanism intermediate between flutter and fibrillation which Doctors Lian and Pinchenzon have called tremulation, a good term if further study justifies its adoption. A further point of interest in research would be to see if other chest leads at other angles might not reveal, even better than S5, circus waves that might be traveling in planes that are not well represented by S5.

PHYSIOLOGY AND PATHOLOGY OF THE HEART AND BLOOD-VESSELS. By John Plesch. Oxford University Press, London, Humphrey Milford, 1937. 188 pages, price $5.25.

The title of this book is somewhat misleading. As indicated in the preface, this work does not pretend to the completeness of a textbook. It is a stimulating general discussion of certain important aspects of the field. It represents an individual viewpoint, based on experimental evidence, on mathematical considerations, on teleological argumentation, and here and there on assumption. It is written by one who has had experience in the field and who must have pondered a great deal on the problems discussed. In general, mechanical factors in the regulation of the circulation are overstressed, often at the expense of established nervous and chemical factors. Several correlations not generally recognized are brought out convincingly.

The first four chapters contain discussion on the mechanical reactions of the blood vessels and on the factors regulating blood volume and blood flow. Chapter V, on the physiological relationship between the arteries and the blood pressure, contains original interpretations. Chapter VI, describing the nature of the regulation of the circulation, is the key which is subsequently applied in the interpretation of some of the problems in pathology, such as circulatory insufficiency, diastolic or volume insufficiency, systolic or force insufficiency, and valvular lesions.

There are several statements which are arbitrary assumption and, on the basis of available evidence, obviously incorrect. The following are examples: "The residual volume of the ventricle is taken as constant" (p. 51). The optimistic statement on arteriosclerosis: "Its progress can be arrested; it can be cured in the early stages and beneficially influenced in more advanced cases" (p. 137). The statement that athletes "show marked calcification of their arteries by the age of 35-40. They are seldom capable of great physical effort in middle life, and many of them die about the age of 50" (p. 143). "Many patients diagnosed on auscultatory evidence as aortic insufficiency, coming to post-mortem from some independent cause before the symptoms of insufficiency develop, show stenosis of the valve without any evidence of insufficiency" (p. 148).

The book is not written for the practicing physician or for the average "specialist." Those who are engaged in the study of the physiology and pathology of cardiovascular problems will find in the book an informative and challenging, though at times one-sided, discussion. It is written from a different angle from any of the recent books on the heart or on the circulation. The author has made an effort "to decide whether a certain formulation in mechanical terms provides a good working hypothesis for the prediction of physiological and pathological events" (p. 83).

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ALLEGEMEINE ELEKTROKARDIOGRAPHIE. von Prof. Dr. Eberhard Koch. Bad Nauheim. 3., verbesserte Auflage. Mit 39 Abbildungen. Dresden und Leipzig, 1937, Verlag von Theodor Steinkopff.

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LAS MIOCARDITIS. Por El Doctor Gregorio N. Martínez, Profesor Titular de la Facultad de Medicina de Córdoba; Miembro de las Academias de Medicina de Río Janeiro, Madrid y Rumanía; en colaboración con los Doctores S. Sonzini Astudillo y C. Deza Cenget. El Ateneo Librería Científica y Literaria. Florida 371—Sucursal; Córdoba 2099. Buenos Aires. 1937.

EXPLORACION DEL CORAZON POR VIA ESOFAGICA. Tesis de Doctorado por el Dr. Alberto C. Taquini. "El Ateneo" Librería Científica y Literaria. Florida 371—Sucursal; Córdoba 2099. Buenos Aires. 1936.

LAVORI DEI CONGRESSI DI MEDICINA INTERNA. Quarantaduesimo Congresso Tenuto in Roma. Nell'Ottobre 1936. Pubblicazione Fatta per Mandato del Consiglio Direttivo dal Prof. Giuseppe Sabatini. RELAZIONI Ia.

FISIOPATOLOGIA DELLO SCOMPENSO CRONICO DI CIRCOLO. Cesa-Bianchi D. e Calabresi M. (Milano). Roma Casa Editrice Luigi Pozzi. 1936-XIV.

Erratum

In the article, "Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs," by Norman E. Freeman, M.D., and Irvine H. Page, M.D., which appeared on page 405 of the October issue of the Journal, the illustrations for Figs. 4, 5, and 6 were incorrectly placed. Figure 4 should have been Fig. 6; Fig. 5 should have been Fig. 4; and Fig. 6 should have been Fig. 5. The legends are correct as numbered and apply correctly to the rearranged illustrations.